Non-glycosylated/non-glycosidic/non-peptidic small molecule PSGL-1 mimetics for the treatment of inflammatory disorders

The present invention relates generally to compounds, compositions and methods for modulating the in vitro and in vivo processes mediated by E-selectin, P-selectin or L-selectin. More specifically, a novel class of small molecule PSGL-1 mimetics and their use are described. The disclosed small molecules comprise trihydroxy phenyl subunits and inhibit selectin-mediated functions potently.

When a tissue has been invaded by a microorganism, is infected or has been damaged, the inflammatory process directs leukocytes and other immune system components to the site of infection or injury. Within this process, leukocytes (white blood cells) play a major role in the engulfment or digestion of microorganisms. Thus, the recruitment of leukocytes to infected or damaged tissue is critical for mounting an effective immune defense. Generally, white blood cells are found circulating through the bloodstream. To migrate from the blood stream into the affected tissue, the white blood cells must be able to recognize the invaded or damaged tissue, be able to bind to the wall of the capillary endothelium near the affected tissue and diffuse through the cell wall of the capillary into the affected tissue. Therefore, leukocytes have to roll onto and then adhere to the endothelial cell wall. This cell adhesion event is one of the most important aspects of the inflammatory response. The first steps of this cell adhesion are mediated by members of the selectin family. The selectin family of vascular adhesion molecules is comprised of three structurally related calcium-dependent carbohydrate binding cell surface proteins, E-, P- and L-selectin. E-selectin is expressed only on inflamed endothelium, P-selectin is expressed on inflamed endothelium as well as on platelets, and has structural similarity to E-selectin. L-selectin is expressed on leukocytes and also has structural similarity to P- and E-selectin.

The selectins are transmembrane proteins and are composed of an amino terminal lectin domain, an epidermal growth factor (EGF)-like domain, a variable number of complement receptor-related repeats, a hydrophobic domain spanning region and a cytoplasmic domain. The binding interactions which lead to the adhesion of the leukocytes appear to be mediated by contact of the lectin domain of the selectins and various carbohydrate ligands on the surface of the leukocytes. All three selectins can bind with low affinity to the carbohydrate sialyl Lewis^x (sLe^x), a glycosyl moiety present on the surface of most leukocytes. A structurally related glycosyl moiety , sialyl Lexis^a (sLe^a), is predominately found on the surface of cancer cells [K. Okazaki et al.; *J. Surg. Res.*; 1998; 78(1); 78-84 and R. P. McEver et al.; *Glycoconjugate Journal*; 1997; 14(5); 585-591]. In case of P-selectin, a distinct high affinity glycoprotein ligand has been described [R.P. McEver; R.D. Cummings; *J.Clin.Invest.*; 1997; 100; 485-492], the so-called PSGL-1 (P-selectin glycoprotein ligand-1), which contributes to a high affinity selectin binding by its sLe^x moiety as well as by parts of its peptide components, in particular sulphated tyrosine residues [R.P. McEver; *Ernst Schering Res. Found. Workshop*; 2004; 44; 137-147]. PSGL-1 is one of the most important selectin ligands binding with highest affinity to P-selectin, but it also binds to E- and L-selectin [G. Constantin; *Drug News Perspect;* 2004; 17(9); 579-586]. It is a homodimeric sialomucin predominantely expressed on leukocytes.

In contrast to their low basal expression, E- and P-selectin expression is upregulated during inflammation, leading to a substantial recruitment of leukocytes into the inflamed tissue. Although selectin-mediated cell adhesion is required for fighting infection, there are various situations in which such cell adhesion is undesirable or excessive, resulting in severe tissue damage instead of repair. In the case of many acute as well as chronic inflammatory disorders [e.g., asthma, chronic obstructive pulmonary disease (COPD), psoriasis, etc.], an association between infiltration of activated leukocytes into the tissue simultaneously with a marked elevation of tissue expression of corresponding adhesion molecules, particularly E- and P-selectin, has been demonstrated.

White blood cell infiltration may also play a role in inflammatory symptoms in the course of transplant and graft rejection. Also the process of blood clotting is further promoted by leukocyte-leukocyte and leukocyte-platelet binding, which occurs because leukocytes

possess both L-selectin and its corresponding ligand PSGL-1 and can thus interact with themselves via PSGL-1, and they can also bind to platelets which carry P-selectin.

Therefore, the inhibition of selectin-mediated cell adhesion offers a promising possibility
5   to interfere with and stop the inflammation cascade at a very early step. Small molecule selectin inhibitors should inhibit all three selectins simultaneously as pan-selectin-antagonists to circumvent possible redundancies between the selectins [M. Sperandio et al.; *Vascular Disease Prevention*; 2004; 1; 185-195].

10   Besides sLe^x/sLe^a, the natural, high affinity ligand PSGL-1 is another template structure for the design of small molecule selectin inhibitors. As compared to sLe^x/sLe^a, PSGL-1 shows high affinity for all three selectins. To find and to detect novel small molecule drugs that compete with PSGL-1 for selectin binding is therefore a promising strategy to develop a novel class of effective pan-selectin antagonists for treating inflammatory disorders.
15   Selectin inhibitors may be designed using selectins as well as a ligand like PSGL-1 as a template structure, since they are intended to inhibit the binding between selectins and PSGL-1 or other ligands with similar binding motifs.

Novel small molecule selectin inhibitors could meet certain requirements to be drug-like
20   and to have potential oral bioavailability. The term drug likeness is described in the literature [Lipinski; *Adv. Drug Dev. Rev.*; 1997; 23; 3-25]. Beside other molecular properties, passively transported molecules are supposed to have a relative molecular weight of less than 500 in order to be drug like. According to these rules it is common to define compounds with a relative molecular weight less than 500 as small molecules,
25   which is a prerequisite for molecules to be drug like and thereby orally bioavailable. Also the presence of a highly polar carbohydrate moiety or a peptidic component is not in accordance with the concept of drug likeness [H. Ulbrich et al.; *Trends Pharmacol. Sci.*; 2003; 24(12); 640-647. D. Slee et al.; *J. Med. Chem.*; 2001; 44; 2094-2107]. Moreover, the desired compounds must be stable during the passage through the gastrointestinal tract so
30   that they can be ingested/absorbed latest by the cells of the small intestines, which is not the case for most glycosidic molecules and peptidic structures. Most structures cited below as typical prior art examples with selectin inhibitory capacity have either high potency

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while being large, non-drug-like molecules with unfavourable ADME properties or low potency while being small to mid-sized sLe^x - or sLe^a- glycomimetics with unfavourable ADME properties.

5   EP1 081 151 A1 discloses novel bioactive compounds for the treatment of abnormal angiogenesis.
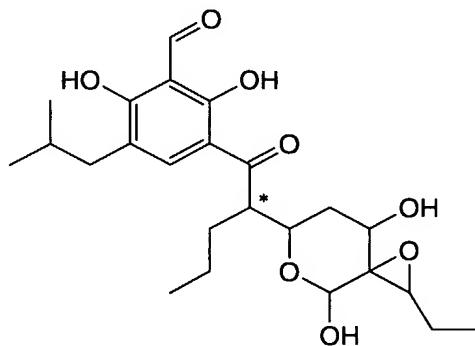
The structures are novel anti-inflammatory substances being also potential inhibitors of
10   VCAM as well as E-selectin expression, but no inhibitors of selectin-mediated binding.

US 6,340,700 B1 provides compounds which have an inhibitory activity against NO-synthase enzymes producing nitrogene monoxide NO and/or an activity which traps the reactive oxygene species (ROS) and which may produce this way favourable effects in
15   treatment of inflammatory diseases. A typical compound is
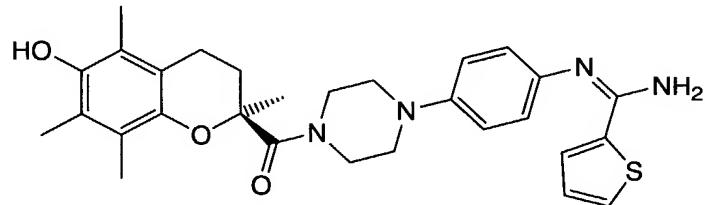
Also mentioned is the preparation of smaller intermediates leading to these compounds. A medical use of these intermediates is not claimed. E.g. one of these intermediates is

20
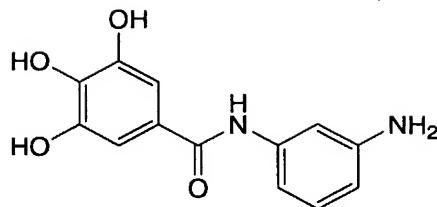
The disalicylates and disalicylate-based C-glycosides of WO 99/29706 act as selectin-ligand structural mimetics in medicaments. They may lack the sialic acid and/or fucose of the natural selectin ligand being sLe^x. A typical compound of the group of carbohydrate free sLe^x - glycomimetics with low to moderate biological activity is
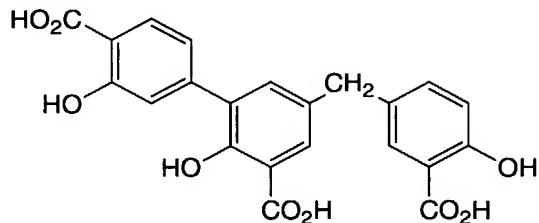

Due to the presence of three polar, possibly charged carboxylic groups, this structure is not in agreement with Lipinski´s rules - as defined before -, indicating a possibly poor oral bioavailability. An additional carbohydrate moiety further reduces the potential of oral bioavailability.

According to WO 03/097658 the compounds for modulating in vitro and in vivo processes mediated by selectin binding are benzyl amino sulfonic acids, which may be linked to carbohydrate or a glycomimetic. The compounds disclosed have mostly activities in the mM range. One of the most potent compounds with a relative molecular weight of 1505 is

- 6 -
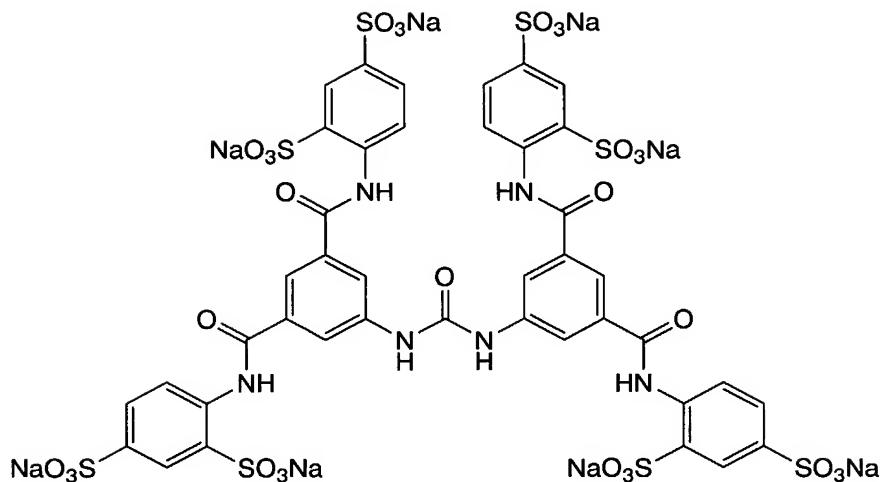
WO 99/29705 describes sLe^x- and sLe^a-glycomimetics, which may be useful in the treatment of selectin-mediated disorders. A typical compound is
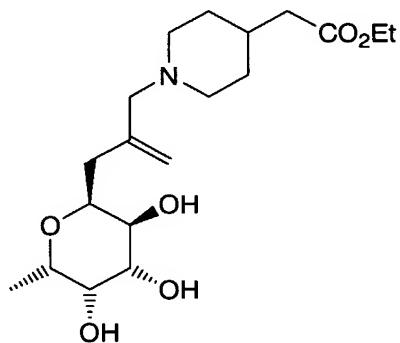
Most of the compounds cover carbohydrate-like structures and are therefore likely to have the typical pharmacokinetic disadvantages associated with carbohydrates. Few non-glycosidic sLe^x – and sLe^a – glycomimetics are described. On average the activities of the disclosed structures are in the mM range.

WO 97/01569 discloses diglycosylated 1,2 diols as mimetics of sLe^x and sLe^a. These glycosidic compounds are large and prone to digestive degradation in the intestine, which both impairs oral bioavailability. An example is

- 7 -
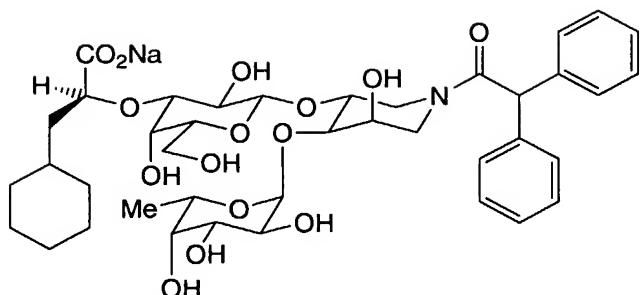
The substituted 5-membered heterocycles of WO 00/33836 exhibit inhibitory activity against E- and P-selectin only. The compounds are sLe^x- glycomimetics. One of the most potent compounds is
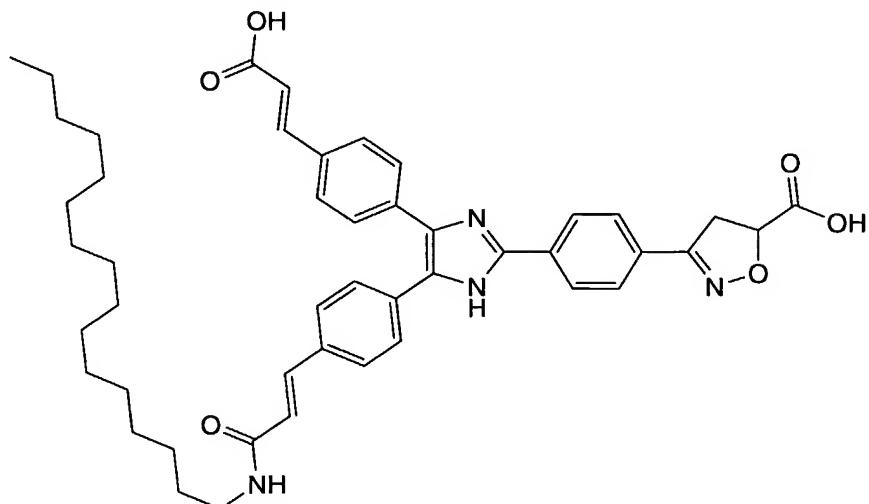
with a relative molecular weight of 773. Clinical development has not been reported for these molecules.

EP 0 758 243 B1 describes Mannopyranosyloxy-phenyl-benzoic acid or similar acids as components in a medicine for treating or preventing diseases, characterized by the binding of E-, P- and/or L-selectin to sLe^x or sLe^a being present on the cell surface through the inhibition of such binding. Besides inflammatory diseases (like psoriasis or rheumatoid arthritis) other diseases like septic shock, reperfusion injury and cancer are mentioned. These molecules also possess a carbohydrate moiety and could therefore have only low bioavailability.

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D. Bock et al., [*New Drugs*, 2003, D04, 28; p. 28] describe the role of selectin antagonists, especially bimosiamose, as inhibitor of selectins being an inflammation target:
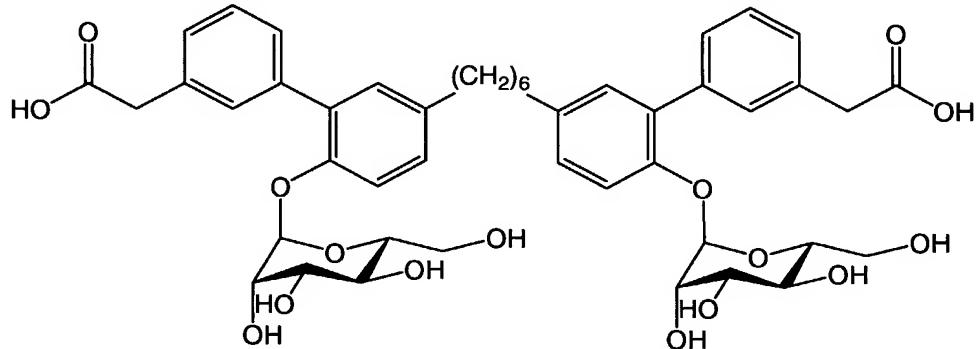

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From EP 0 840 606 B1 compounds like bimosiamose are known, e.g., 1,6-Bis-[3-(carb-oxymethylphenyl)-4-(2-α-D-mannopyranosyloxy)phenyl]hexan and derivatives thereof including heptan, butan and pentan derivatives. Again, their use for inhibiting the selectin binding to sLe^x or sLe^a is mentioned. Bimosiamose and related compounds have been

10   developed originally as sLe^x- and sLe^a-glycomimetics. However, recent investigations support the hypothesis that bimosiamose can be considered as PSGL-1 mimetic [E. Aydt, G. Wolff; *Pathobiology*; 2002-2003; 70; 297-301]. Bimosiamose has a relative molecular weight of 862 and covers two mannose units, which presumably prevents the molecule to be orally bioavailable. This seems to be the only selectin inhibitor, which is currently in

15   clinical trials. Yet, these molecules possess even more than one carbohydrate moiety and are known to lack oral bioavailability.

A different method for inhibiting the binding between a first cell having a selectin and a second cell having a ligand for selectin in vitro is described in EP 0 902 681 B1 in

20   permitting a covalently cross-linked lipid composition to interact with the first cell. A proportion of the lipids has an attached saccharide like fucooligosaccharides, lactose, or an acidic monosaccharide, further proportions are cross-linked and a proportion without attached saccharides has an acidic group being negatively charged at neutral pH. These lipid compositions are used in local alterations in the adherence of leukocytes or cancer

25   cells to vascular endothelium, platelets or lymphatic tissue. Since these compositions are covalently cross-linked, they will resemble multimers with a relative molecular weight,

which by far exceeds 500. Moreover, they contain as well carbohydrate moieties. All these properties render oral bioavailability highly improbable.

WO 2004/018502 describes derivatives of compounds which bind selectively to human P-selectin being peptide containing structures with Glu-Trp-Val-Asp-Val consensus motif to which gallic acid or 1,3,5- benzenetricarboxylic acid at the N- terminus may be added. In addition to the use of such compounds in therapeutic or diagnostic methods to treat inflammatory disorders is mentioned. The necessity to consider PSGL-1 as template structure for developing high affinity selectin inhibitors is described. The type of biological in vitro assays they are using for compound assessment also reflects this. The molecules described have high inhibition potency against human P-selectin, but not against E- and L-selectin. However, their molecular and biological properties render them most probably not orally biovailable. They are unlikely to pass the digestive tract due to their peptidic moieties, which will be degraded by peptidases. In case traces should reach the small intestines, they will probably not be absorbed by passive transport due to their high molecular weight. The most potent compounds have relative molecular weights over 700 and can therefore no longer be considered as small molecule drugs. Two typical substituents are

and
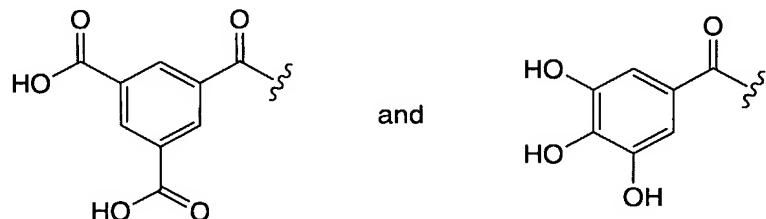
whereby
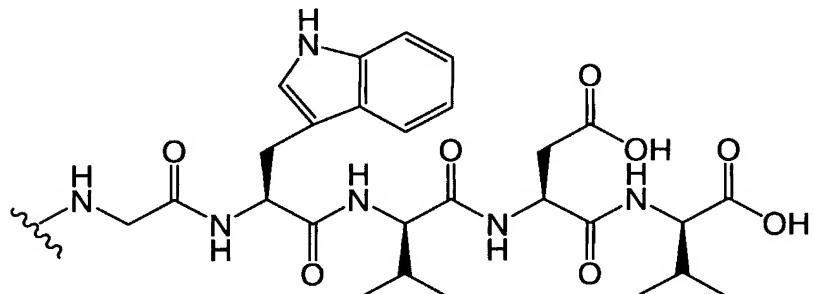
is a typical peptide entity.

WO 01/89531 provides methods for identifying agents which interact with (activate or inhibit) the crystal and three-dimensional structures of a) the lectin and EGF-like (LE) domains of P-selectin, of b) P-selectin LE and E-selectin LE each complexed with sLe^x,

5   and c) P-selectin LE complexed with a functional fragment of the PSGL-1 peptide modified by both tyrosine sulfation and sLe^x.

In such a very complex pharmaceutical field, there is a strong medical need in the art for indentifying novel kinds of inhibitors of selectin-mediated function, e.g. of selectin-

10   dependent cell adhesion, and for the development of methods employing such compounds to inhibit conditions associated with selectin-ligand interaction. Most of the available anti-inflammatory pharmaceutical therapies, which are available on the market comprise mostly corticosteroids or NSAIDs (non steroidal anti-inflammatory drugs) which have several serious drawbacks/side effects, and target different steps of the inflammatory cascade.

15   Unlike this, inhibiting the selectin function is a therapeutic concept intervening the inflammation cascade at a very early stage. Almost all promising selectin inhibitors so far failed to become marketed drugs, not at least because of their low biological activity and /or high molecular weight that causes problems in their absorption-distribution-metabolism-excretion (ADME) behaviour and thus in oral bioavailability which is required

20   for the treatment of most inflammatory disorders like rheumatoid arthritis, septic shock, atherosclerosis, reperfusion injury and many others.

Most of the compounds published in the field of selectin inhibitors are peptide- and/or carbohydrate-bearing structures, which are prone to degradation and modification by

25   peptidases and/or glycosidases. Carbohydrate-bearing structures have further disadvantages such as high molecular weight, high degree of chirality, anomericity, and low probability of transport through lipid bilayers. Similar disadvantages are known for peptide-bearing compounds. Thus, these compounds cannot be considered as small and drug-like molecules, a prerequisite for the development of orally bioavailable selectin

30   inhibitors and drugs in general to be marketed.

Few non-glycosidic and non-peptidic compounds have been described in this field, which are molecules with high relative molecular weight and/or low biological activity. Almost all compounds have been designed on the basis of sLe^x and sLe^a and are therefore glycomimetics. However, the concept of designing sLe^x- and sLe^a-glycomimetics to treat inflammatory disorders has not proven to be successful to date.

Object of the invention is to provide novel small molecules, especially non-glycosylated/non-glycosidic and non-peptidic compounds, which are able to potently inhibit selectin-mediated processes and which have less negative side effects during their in vitro or in vivo application than prior art compounds.

Unlike most of these glycomimetics, the inventive compounds are not prone to glycosidases or peptidases. Most of the selectin inhibitors developed so far are sLe^x- or sLe^a-glycomimetics. This invention, however, provides novel potent small and drug like selectin inhibitors that have been invented on the basis of PSGL-1-like biological in vitro assays. A bioassay has been established implying a PSGL-1-substitute as a selectin-ligand and P-, E-, or L-selectin chimera as binding molecule/receptor. The PSGL-1-substitute used is sLe^x-Tyrosin-sulfate-polymer. Tyrosin-sulfate residues as well as sLe^x-residues have been covalently linked to a polyacrylamid matrix where they are statistically distributed. This technique to mimic the mucin-like molecule PSGL-1 and structurally related ligands is widely used and usage of sLe^x-Tyrosin-sulfate-polymer gives very good selectin-binding results [N. V. Bovin; *Biochem Soc Symp.*; 2002;(69):143-60. N. V. Bovin; *Glycoconj. J.*; 1998; 15(5); 431-46. T.V. Pochechueva et al.; *Bioorg Med Chem Lett.*; 2003;13(10);1709-12. G. Weitz-Schmidt et al.; *Anal. Biochem.*;1996; 238; 184-190]. Also, this technique has been used to establish an assay in WO 2004/018502, but with the restriction, that the carbohydrate moiety of the ligand is not sLe^x, but sLe^a. sLe^a is a ligand which is not generally known to be involved in physiological PSGL-1 binding and has not been described as carbohydrate moiety of PSGL-1, unlike sLe^x. Furthermore, the said molecules should show a good bioavailability when applied as an active ingredient in a medicine.

The present invention provides pharmaceutical compositions comprising at least one
compound having the general structure of formulas (Ia) or (Ib) and a pharmaceutically
acceptable carrier which is useful in medicine
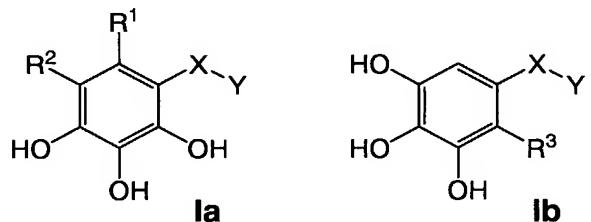
wherein the symbols, indices and substituents have the following meaning

R^1=H, CN, NO_2, CF_3, F, Cl, Br, I, CH_3

R^2=H, CN, NO_2, CF_3, F, Cl, Br, I, CH_3, Et, n-Pr, i-Pr, n-Bu, t-Bu, phenyl, thienyl,
furyl, thiazolyl and

either R^1 or R^2 must be H

R^3=H, CN, NO_2, CF_3, F, Cl, Br, I, CH_3, Et, n-Pr, i-Pr, n-Bu, t-Bu, phenyl, thienyl,
furyl, thiazolyl

-X- =

(a)
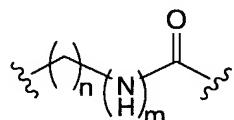
with m = 0,1; n = an integer from 1 to 6

(b)
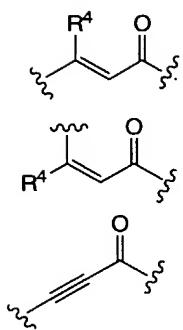
with R^4 being H, CH_3, CH_2CH_3

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c)

(E or Z double bond)
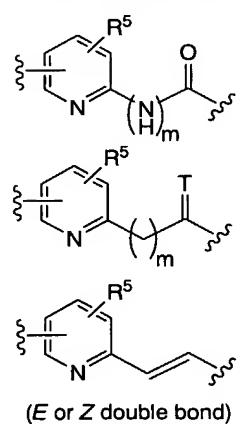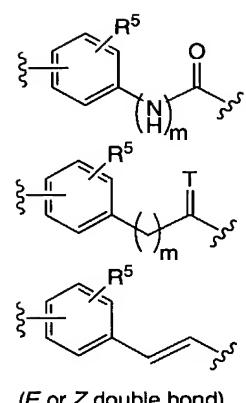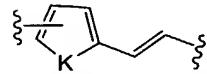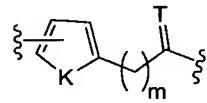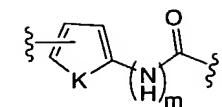
(E or Z double bond)

(*E* or *Z* double bond)
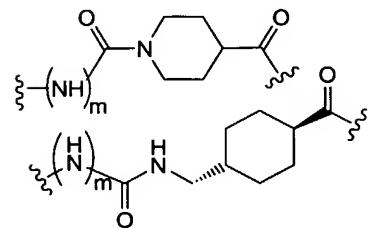
with R^5 being H, NO_2, CF_3, F, Cl, Br, I, CN, CH_3, NH_2, NHAlkyl, NHAryl, NHAcyl and -K- being -S- or -O-

and T being O, S or [H,H]

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(d)
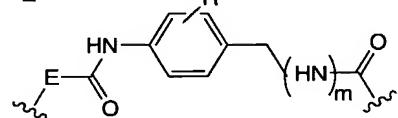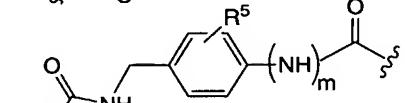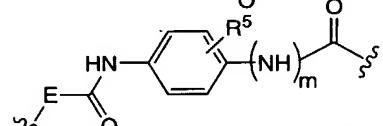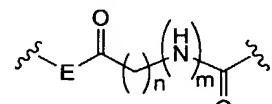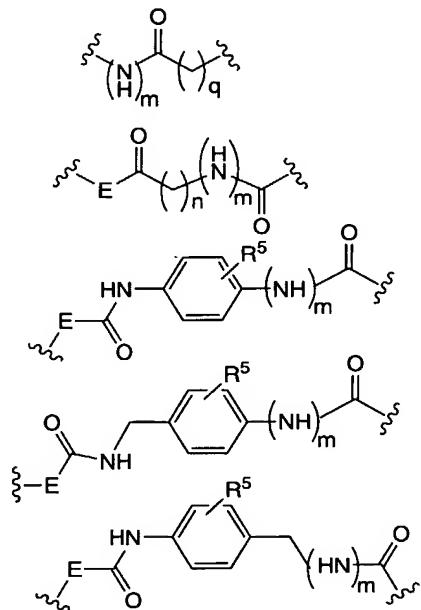
with -E- being $-(CH_2-)_k NH-$ and k=0, 1, 2, 3 and with q being an integer from 1 to 6

-Y =
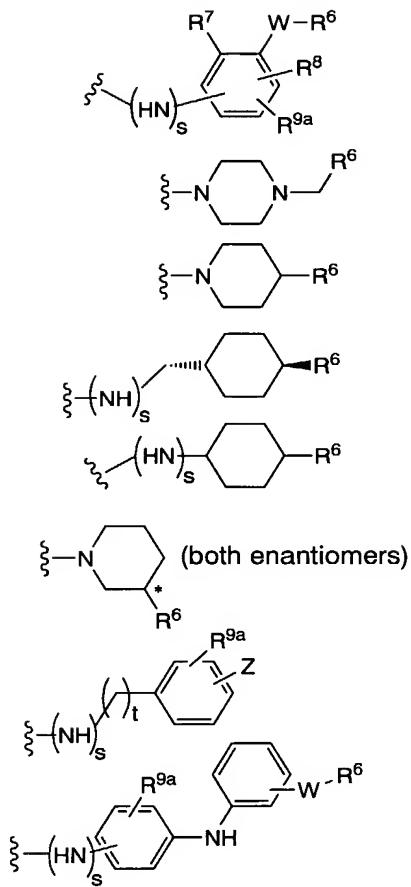
with s being 0 or 1,

R^6 being CO_2H, CO_2Alkyl, CO_2Aryl, CO_2NH_2, $CO_2Aralkyl$, SO_3H, SO_2NH_2, $PO(OH)_2$, 1-H-tetrazolyl-, CHO, $COCH_3$, CH_2OH, NH_2, NHAlkyl, N(Alkyl)Alkyl', OCH_3, CH_2OCH_3, SH, F, Cl, Br, I, CH_3, CH_2CH_3, CN, CF_3

R^7 independently from R^6 being H, CH_3, CH_2CH_3, CF_3, F, Cl, Br, I, CN, NO_2 and

R^8 independently from R^6 and R^7 being H, CH_3, CH_2CH_3, CF_3, F, Cl, Br, I, CN, NO_2, R^6

R^{9a} being H, NO_2, CF_3, F, Cl. Br, I, CN, CH_3, OCH_3, SH, NH_2

t being 0,1,2

and -W- = -(CH$_2$-)$_v$, cis-CH=CH- or trans-CH=CH-, and v being 0,1,2;

in case that R^6 = NH$_2$ R^7 or R^8 or R^{9a} must not be H;

in case that -W- is cis-CH=CH- or trans-CH=CH-, R^6 must not be NH$_2$ or SH;

-Z =

(both enantiomers, each)
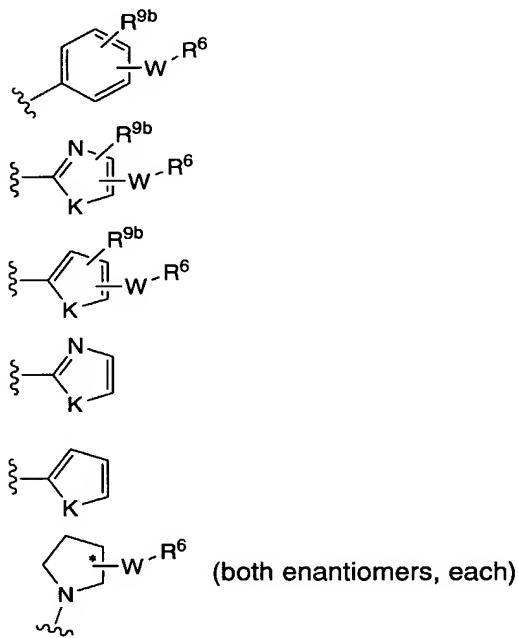
-W-R^6

R^{9b} independently from R^{9a} being H, NO$_2$, CF$_3$, F, Cl. Br, I, CN, CH$_3$, OCH$_3$, SH, NH$_2$,

or the pharmaceutically acceptable salts, esters or amides and prodrugs of the above identified compounds of formulas (Ia) or (Ib).

Preferred pharmaceutical compositions comprise compounds of formulas (A1), (B1), (A2) or (B2)

A1

B1

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A2   B2
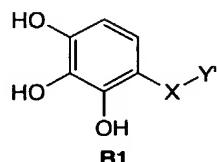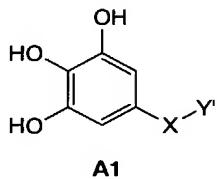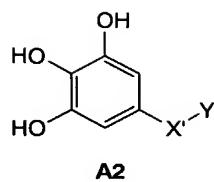
wherein -X- and -Y are like defined above and wherein -X'- is

m=0,1

5   and wherein -Y' is

(Q=CH, N)
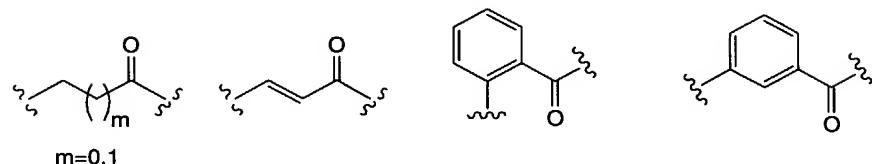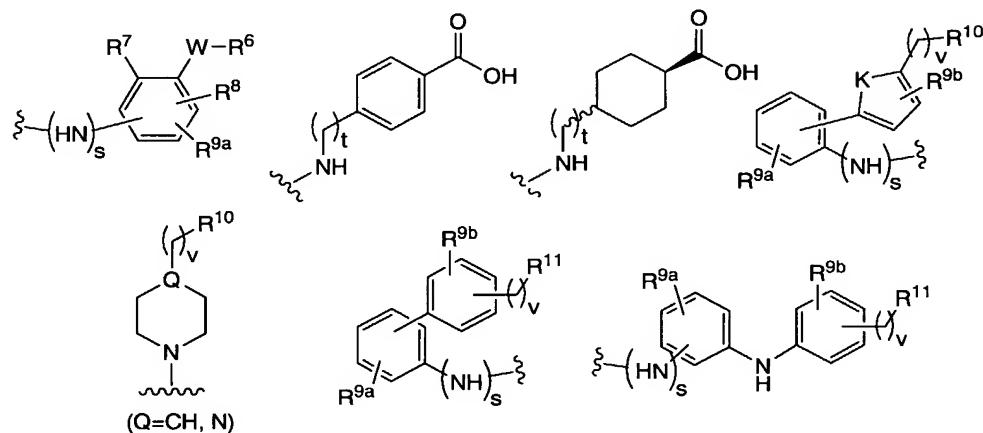
with R^{10} being CO$_2$H, CO$_2$alkyl, CO$_2$aryl, CO$_2$NH$_2$, CO$_2$aralkyl, CH$_2$SO$_3$H, CH$_2$SO$_2$NH$_2$, CH$_2$PO(OH)$_2$, 1-H-tetrazolyl, CHO, COCH$_3$, CH$_2$OH, CH$_2$NH$_2$,

10   CH$_2$NHalkyl, CH$_2$N(alkyl)alkyl', CH$_2$OCH$_3$, CH$_2$SH,

R^{11} being CO$_2$H, CO$_2$alkyl, CO$_2$aryl, CO$_2$NH$_2$, CO$_2$aralkyl, SO$_3$H, SO$_2$NH$_2$, PO(OH)$_2$, 1-H-tetrazolyl, CHO, COCH$_3$, OH, NH$_2$, NHalkyl, N(alkyl)alkyl', OCH$_3$, SH

15 Further particularly preferred pharmaceutical compositions comprise compounds of formulas (C) and (D)
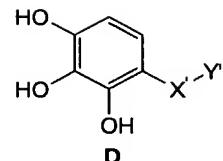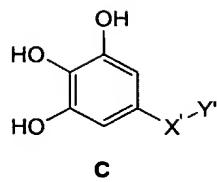
wherein -X'- and -Y' are like defined above.

5   These compounds (C) and (D) are also new compounds for themselves.

All compounds as described before present the ability of inhibiting cell adhesion and inhibit selectin- as well as PSGL-1-like mediated binding. The compounds have the ability to inhibit the interaction of selectins with sLe^x/sLe^a and also the interaction between

10   selectins and tyrosinesulfate residues. Therefore they are useful for the treatment of acute and chronic inflammatory disorders, as well as other medical conditions where selectin mediated processes play a role.

The term "pharmaceutical" includes also diagnostic applications.

15   The term "pharmaceutical" includes also prophylactic applications in order to prevent medical conditions where selectin mediated processes play a role.

The term "pharmaceutical" includes also applications, where compounds of the present invention may be used as vehicles for drug targeting of diagnostics or therapeutics.

20   In a further preferred variant the invention provides pharmaceutical compositions comprising at least one compound of formula (A1), (A2), (B1), (B2), (C) or (D).

The present invention further provides a method of inhibiting the binding of P-selectin, L-selectin or E-selectin to sLe^x or sLe^a and tyrosinesulfate residues comprising the step of

25   administering to a patient an effective amount of at least one compound having the

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structure of formulas (Ia) or (Ib) to inhibit the binding of P-, E- or L-selectin to sLe^x or sLe^a and tyrosinesulfate. It has been found that compounds having the formulas (Ia) or (Ib) shown above act to inhibit E-, P- or L-selectin binding.

5   As used herein the term "alkyl" shall mean a monovalent straight chain or branched chain group of 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl and the like.

10   The term "aryl" shall mean carbocyclic and heterocyclic aromatic groups including, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, fluorenyl, (1,2)-dihydronaphthyl, indenyl, indanyl, thienyl, benzothienyl, thienopyridyl and the like.

       The term "aralkyl" (also called arylalkyl) shall mean an aryl group appended to an alkyl
15   group including, but not limited to, benzyl, 1-naphthylmethyl, 2-naphthylmethyl, fluorobenzyl, chlorobenzyl, bromobenzyl, iodobenzyl, alkoxybenzyl (wherein "alkoxy" means methoxy, ethoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy an the like), hydroxybenzyl, aminobenzyl, nitrobenzyl, guanidinobenzyl, fluorenylmethyl, phenylmethyl(benzyl), 1-phenylethyl, 2-phenylethyl, 1-naphthylethyl and the like.

20

       The term "pharmaceutically acceptable salts, esters, amides and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with tissues of patients without undue toxicity,
25   irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or
30   by separately reacting the purified compounds in its free form with a suitable inorganic or

organic acid or base and isolating the salt thus formed. Representative salts of the compounds of the present invention include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate,

5   mesylate, glucoheptonate, lactiobionate, laurylsulphonate salts and the like. These may include cations based on the alkali and alkalineearth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as non-toxic ammonium, quaternary ammonium   and   amine   cations   including,   but   not   limited   to,   ammonium, tetramethylammonium,   tetraethylammonium,   methylamine,   dimethylamine,

10   trimethylamine, triethylamine, ethylamine, and the like.

Examples of the pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5, C_6 and C_7 cycloalkyl esters as well

15   arylalkyl esters such as, but not limited to benzyl. C_1, C_2, C_3, C_4, C_5 and C_6 alkyl ester are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of compounds of this

20   invention include amides derived from ammonia, primary C_1, C_2, C_3, C_4, C_5 and C_6 alkyl amines and secondary C_1, C_2, C_3, C_4, C_5 and C_6 dialkyl amines wherein the alkyl groups are straight or branched chains. In the case of secondary amines the amine may also be in the form of a 5 or 6 membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1, C_2 and C_3 alkyl primary amides and C_1 to C_2 dialkyl secondary amides

25   are preferred. Amides of the compounds of the present invention may be prepared according to conventional methods.

The term "prodrug" refers to one or more compounds that are rapidly transformed *in vitro* and from a non-active to active state *in vivo* to yield to the parent compound of the above

30   formulas (Ia) or (Ib), for example by hydrolysis in blood or *in vivo* metabolism.

It is also contemplated that pharmaceutically active compositions may contain a compound of the present invention or other compounds that inhibit or compete with E-selectin or P-selectin or L-selectin binding.

5   Pharmaceutically active compositions of the present invention comprise a pharmaceutically acceptable carrier and a compound of formulas (Ia) or (Ib), whereby a pharmaceutically acceptable carrier can also be a medically appropriate nano-particle, dendrimer, liposome, microbubble or polyethylene glycol (PEG). The pharmaceutical compositions of the present invention may include one or more of the compounds having

10   the above structure (Ia) or (Ib) formulated together with one or more, physiologically acceptable carriers, adjuvants or vehicles, which are collectively referred to herein as carriers, for parenteral injection, for oral administration in solid or liquid form, for rectal or topical administration and the like.

15   The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, intradermaly or subcutaneously), intracisternally, intravaginally, interperitoneally, locally (powders, ointments or drops), or as a buccal or by inhalation (nebulized, or as nasal sprays).

20   Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, stabilizers, antioxidants, preservatives (e.g. ascorbic acid, sodium sulfite, sodium hydrogene sulfite, benzyl alcohol, EDTA), dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solution or dispersion. Examples of suitable aqueous and nonaqueous carriers,

25   diluents, solvents or vehicles include water, ethanol, polyol, (propylene glycol, polyethylene glycol, glycerol and the like), suitable mixtures thereof, vegetable oils (such as olive or canola oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for examples, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

30

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of the actions of microorganisms can be ensured by various antibacterial and antifungal agents, for examples, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for examples sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for examples aluminium monostearate and gelatin.

If desired, and for more effective distribution, the compounds can be incorporated into slow or timed release or targeted delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile water, or some other sterile injectable medium immediately before use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound or a prodrug ester is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (i) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (ii) binders, as for example, carboxymethylcellulose, alginates, gelatine, polyvinylpyrrolidone, sucrose and acacia, (iii) humectants, as for example, glycerol, (div disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, aliginic acid, certain complex silicates and sodium carbonate, (v) solution retarders, as for examples, paraffin, (vi) absorption accelerators, as for example, quaternary ammonium compounds, (vii) wetting agents, as for examples, cetyl alcohol and glycerol monostearate, (viii) adsorbents, as for example, kaolin and bentonite, and (ix) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

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Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatine capsules using excipients as lactose or milk sugars as well as high molecular polyethylene glycols and the like. Solid dosage forms such as tablets, dragées, capsules, pills and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such compositions that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, cannola oil, caster oil and sesame seed oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like. Besides such inert diluents, the compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweeting, flavouring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar, tragacanth or mixtures of these substances and the like.

Compositions for rectal administrations are preferably suppositories, which can be prepared by mixing the compounds of the present invention with suitable nonirritating

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excipients or carriers such as cacao butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore melt in the rectal or vaginal cavity and release the active component. Dosage forms for topical administration of a compound of this invention include ointments, powder, sprays and

5   inhalants.

The active component is admixed under sterile conditions with a physiologically acceptable carrier and any needed preservatives, buffers or propellants as may be required. Ophthalmic formulations, eye ointments, suspensions, powder and solutions are also contemplated as being within the scope of this invention.

10

The compounds of the present invention can also be incorporated into or connected to liposomes or administrated in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium.

15   Any non-toxic, physiologically acceptable metabolized lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to the selectin binding inhibitors of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are well known in the

20   art.

Non-parenteral dosage forms may also contain a bioavailability enhancing agent (e.g. enzyme inhibitors, antioxidants) appropriate for the protection of the compounds against degradation. Actual dosage levels of active ingredient in the composition of the present

25   invention may be varied so as to obtain an amount of active ingredient that is effective to obtain the desired therapeutic response for a particular composition and method of administration. The selected dosage level, therefore, depends on the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors. The total daily dosage of the compounds on this invention administered to a host in

30   single or divided doses may be in the range up to 50 mg per kilogram of body weight. Dosage unit compositions may contain such submultiples thereof as may be used to make

up the daily dosage. It will be understood, however, that the specific dose level for any particular patient, whether human or other animal, will depend upon a variety of factors including the body weight, general health, sex diet, time and route of administration, rates of absorption and excretion, combination with other drugs and the severity of the particular

5   disease being treated.

In particular, the compounds of the present invention may be used to treat a variety of diseases relating to inflammation and cell-cell recognition and adhesion. For example, the compounds of the present invention may be administrated to a patient to treat COPD, acute respiratory distress syndrome (ARDS), Crohn's disease, septic shock, chronic

10   inflammatory diseases such as psoriasis, atopic dermatitis, and rheumatoid arthritis, and reperfusion tissue injury that occurs following heart attacks, strokes, atherosclerosis, and organ transplants, traumatic shock, multi-organ failure, autoimmune diseases like multiple sclerosis, asthma and inflammatory bowel disease. In each case, an effective amount of the compounds of the present invention is administered either alone or as part of a

15   pharmaceutically active composition to a patient in need of such treatment. It is also recognized that a combination of the compounds may be administered to a patient in need of such administration. The compounds of the present invention may also be administered to treat other diseases that are associated with cell-cell adhesion. As the present compounds inhibit the binding of E-selectin or P-selectin or L-selectin, any disease that is related to

20   this interaction may potentially be treated by the inhibition of this binding interaction.

In addition to being found on some white blood cells, sLe^a is found on various cancer cells, including lung and colon cancer cells. It has been suggested that cell adhesion involving sLe^a may be involved in the metastasis of certain cancers and inhibitors of sLe^a binding

25   might be useful in treatment of some forms of cancer.

Many of the compounds of the present invention may be synthesized according to the following general synthetic schemes.

SCHEME 1
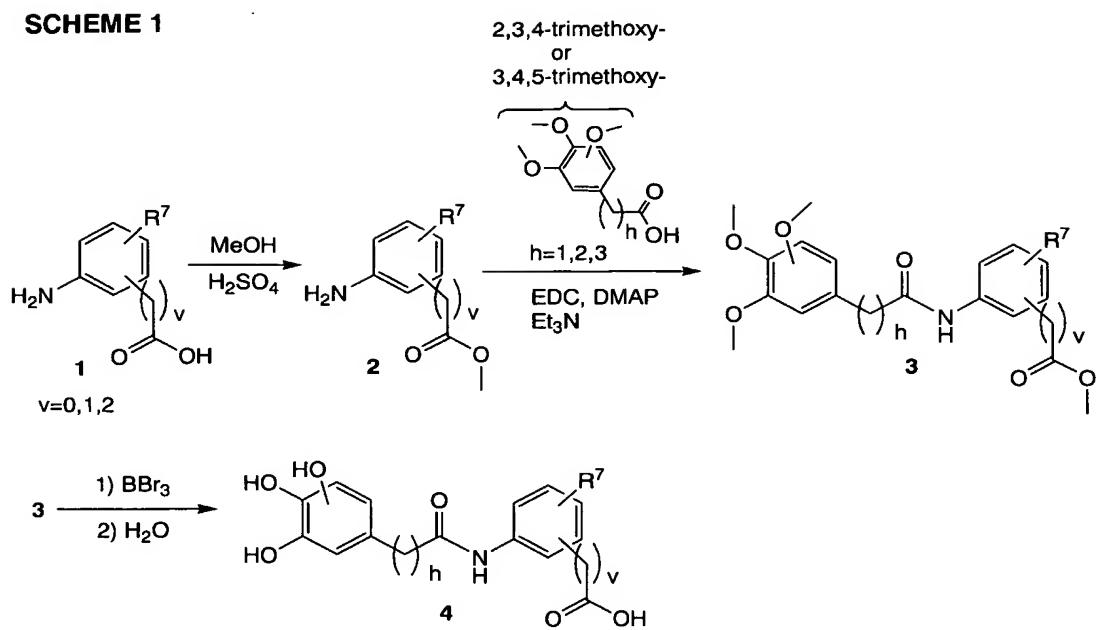
In SCHEME 1 an amino acid of type (1) is reacted to the corresponding methyl ester (2) under heating with acidic methanol. Ester (2) is reacted with a trimethoxy-phenyl-alkylic

5   acid under state-of-the-art conditions (i.e. N'-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC), triethylamine and 4-dimethylaminopyridine (DMAP) in a chlorinated solvent) to the amide (3). Alternatively diisopropyl carbodiimide (DIC) and hydroxybenzotriazole (HOBt) may be used for this reaction step. Amide (3) is converted to acid (4) by treating it with an excess of boron tribromide at −78°C up to rt in a halogenated

10 solvent followed by aqueous workup. However, in some cases it may be necessary to hydrolize the ester (3) with i.e. aqueous lithium hydroxide in acetonitrile before treating it with boron tribromide. The synthesis sequence shown in SCHEME 1 leading to compounds like (4) is not only reduced to the Y-H building blocks like (1) but may be generally applied to all other Y-H type building blocks leading to compounds of type (A1),

15 (A2), (B1) and (B2) as shown in the paragraph before.

SCHEME 2
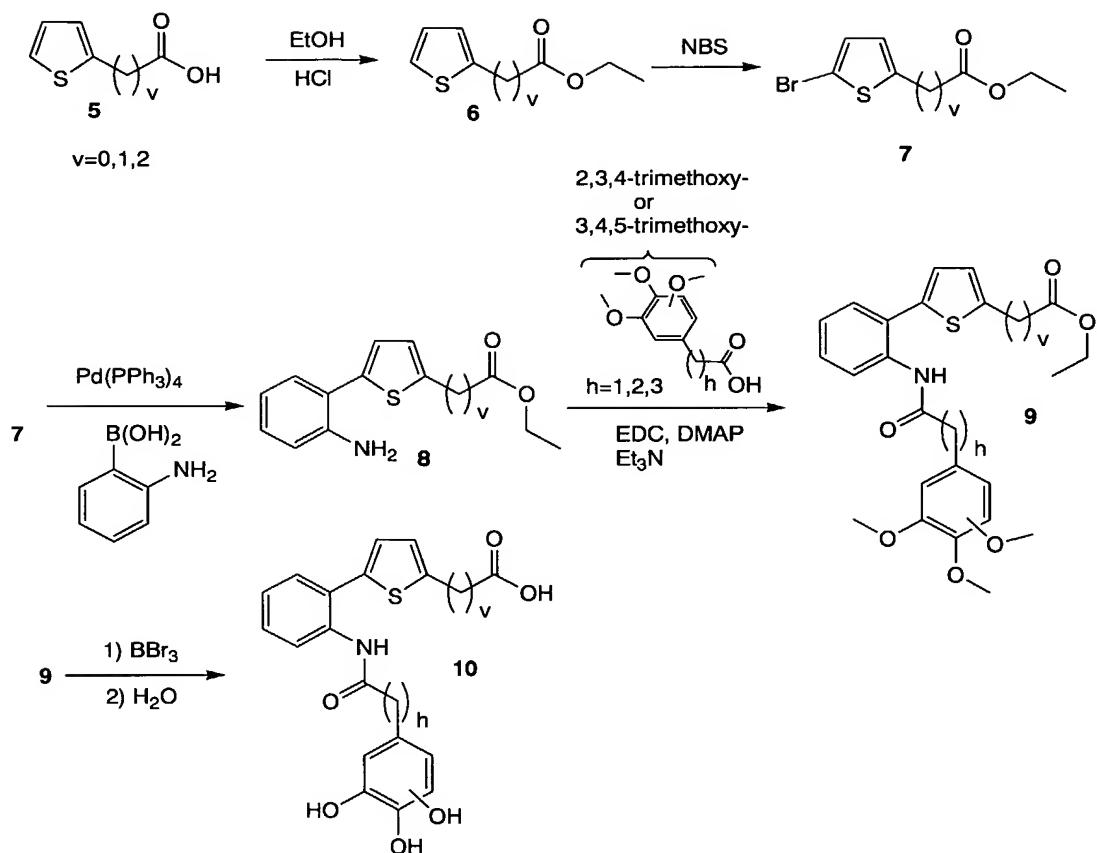
In SCHEME 2 a carboxy substituted thiophene like (5) is reacted to the corresponding
ethyl ester (6) under heating in acidic ethanol. Ester (6) is brominated with N-
bromosuccinimide in anhydrous chloroform and glacial acetic acid to give (7) which is
further reacted with 2-Amino-benzeneboronic acid under a state-of-the-art Suzuki
transformation (i.e. Tetrakis(triphenylphosphine)-palladium, aqueous sodium carbonate,
ethanol, toluene) to the biaryl (8). Biaryl (8) is reacted with a trimethoxy-phenyl-alkylic
acid, EDC, triethylamine and DMAP in a chlorinated solvent to the amide (9).
Alternatively DIC and HOBt may be used for this reaction step. Amide (9) is converted to
acid (10) by treating it with an excess of boron tribromide at –78°C up to rt in a
halogenated solvent followed by aqueous workup. However, in some cases it may be
necessary to hydrolize the ester (9) with i.e. aqueous lithium hydroxide in acetonitrile
before treating it with boron tribromide.

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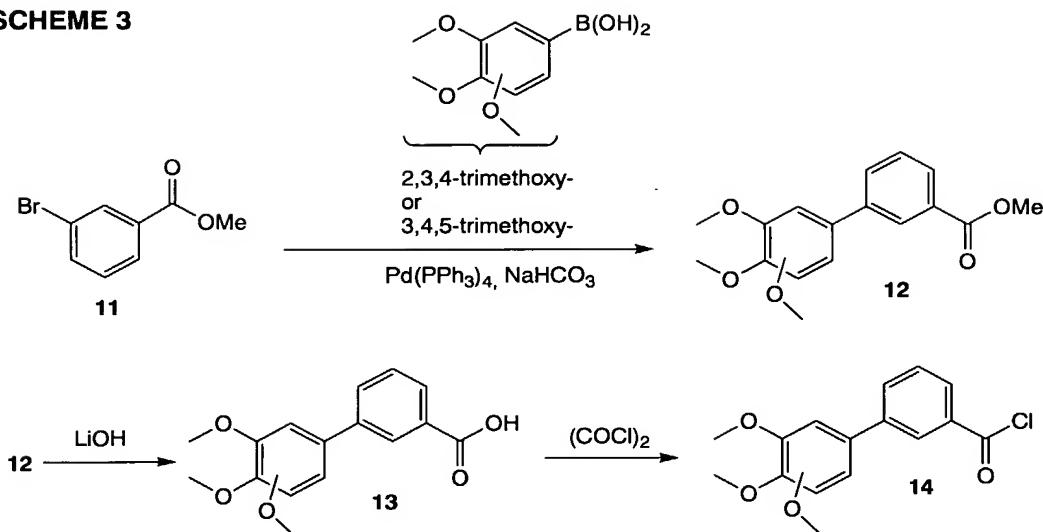
SCHEME 3

In SCHEME 3 Methyl-3-bromobenzoate (11) is reacted under inert conditions with a
Trimethoxyphenylboronic acid under Suzuki-type basic conditions (Pd(PPh$_3$)$_4$ and aqueous
sodium bicarbonate in dimethoxymethane) to a biphenyl of type (12) which is further
hydrolized with aqueous lithium hydroxide in acetonitrile to give the corresponding
carboxylic acid (13) which was converted to building block of type (14) by reaction with
oxalyl chloride in anhydrous dichloromethane.

SCHEME 4
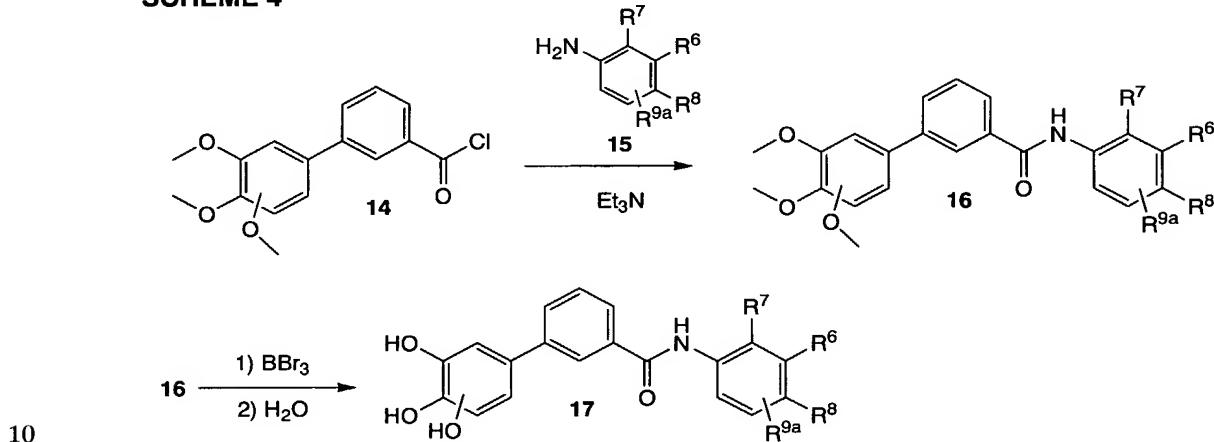
In SCHEME 4 an acid chloride like (14) is reacted with an aniline of general type (15)
under basic conditions (triethylamine in a chlorinated solvent) to form the anilide (16).

Alternatively pyridine may be used for this reaction step. Anilide (16) is converted to trihydroxyphenyl (17) by treating it with an excess of boron tribromide at −78°C up to rt in a halogenated solvent followed by aqueous workup.

In case that R^6 and/or R^8 contain carboxylic acid functionalities, those are protected as
their corresponding methyl or ethyl esters before and hydrolized afterwards to release the carboxylic acid functionalities. The ester hydrolysis was done whether with LiOH in MeCN or THF/MeOH or under treatment with BBr$_3$ in followed by addition of water.

The synthesis sequence shown in SCHEME 4 leading to compounds like (17) is not only reduced to X-Y-H and Y-H building blocks like (15) but may be generally applied to all
other X-Y-H and Y-H type building blocks leading to compounds of type (A1), (A2), (B1) and (B2) as shown in the paragraphs before.
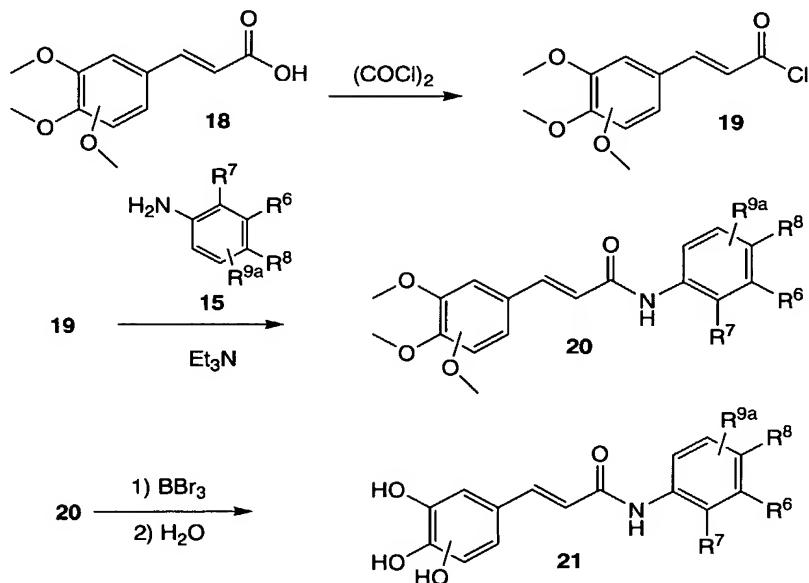
SCHEME 5

For compounds of type (21) containing a trihydroxy cinnamic moiety a synthesis sequence
according to SCHEME 5 may be applied. A trihydroxy cinnamic acid of type (18) is converted to the corresponding acid chloride (19) by reaction with oxalyl chloride in anhydrous dichloromethane. The acid chloride like (19) is reacted with an aniline of general type (15) under basic conditions (triethylamine in a chlorinated solvent) to form

the anilide (20). Alternatively pyridine may be used for this reaction step. Following treatment of (20) with an excess of boron tribromide in dichloromethane at −78°C up to rt and aqueous workup provides the desired compound (21).

SCHEME 6
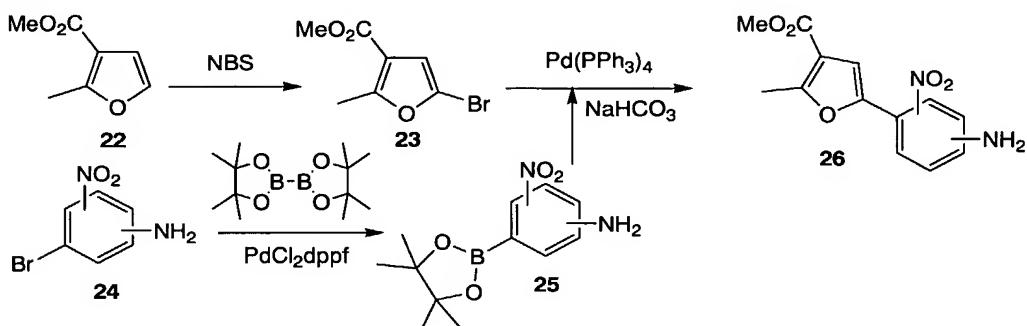
In SCHEME 6 the generation of building block (26) is outlined, whereby the furane (23) is available by NBS-bromination of methyl furoate (22) and pinacolyl borane of type (25) is available by Pd-catalyzed boration of anilines like (24). Suzuki-type coupling of (23) and (25) with Pd(PPh$_3$)$_4$ leads to biaryls of type (26).
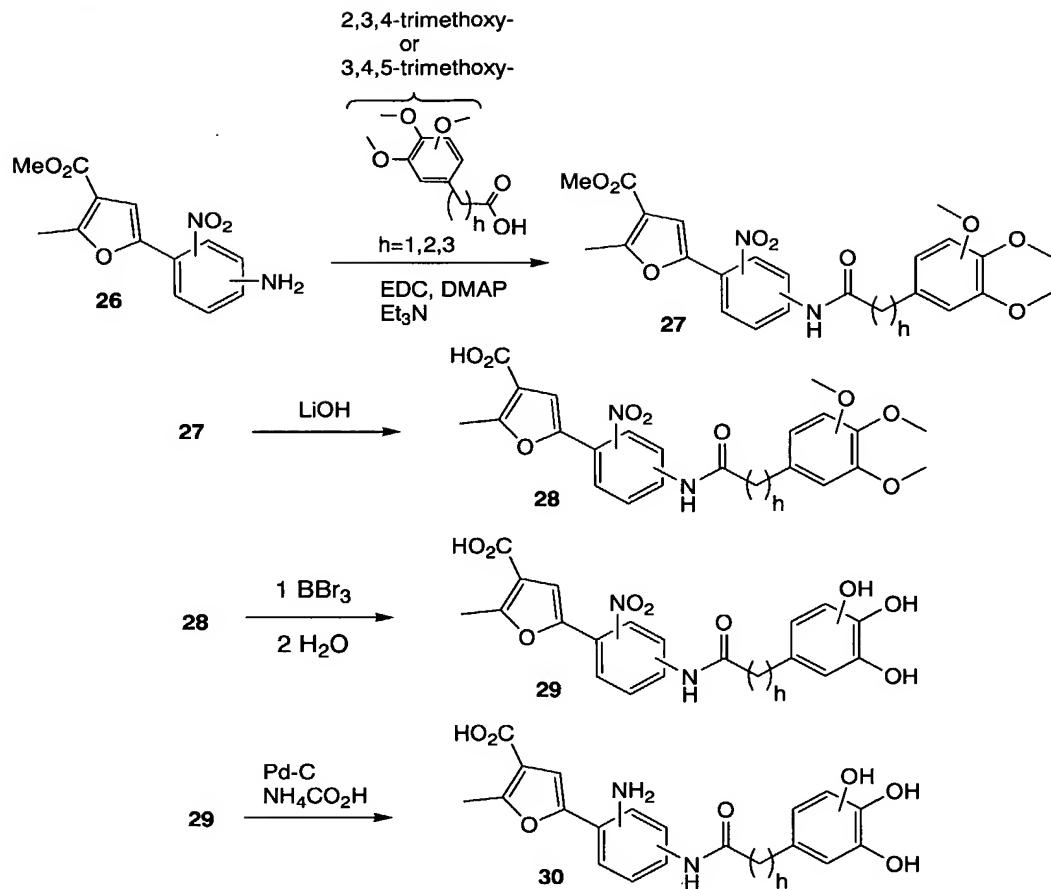
SCHEME 7

In SCHEME 7 a biaryl of type (26) is reacted with a trimethoxy-phenyl-alkylic acid under state-of-the-art conditions (i.e. N'-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC),

5   triethylamine and 4-dimethylaminopyridine (DMAP) in a chlorinated solvent) to the amide of type (27). Alternatively diisopropyl carbodiimide (DIC) and hydroxybenzotriazole (HOBt) may be used for this reaction step. (27) is then hydrolized to acid of type (28) whether with LiOH in MeCN or THF/MeOH. Treatment of (28) with with an excess of boron tribromide in dichloromethane at –78°C up to rt and aqueous workup provides

10   compounds (29) which are finally hydrogenated with Pd on Carbon and ammonium formate to the desired compounds of general structure (30).

The present invention is furthermore illustrated by the following representative examples.

15

EXAMPLE 1

{3-[3-(2,3,4-Trihydroxy-phenyl)-propionylamino]-phenyl}-acetic acid (34)

SCHEME 8
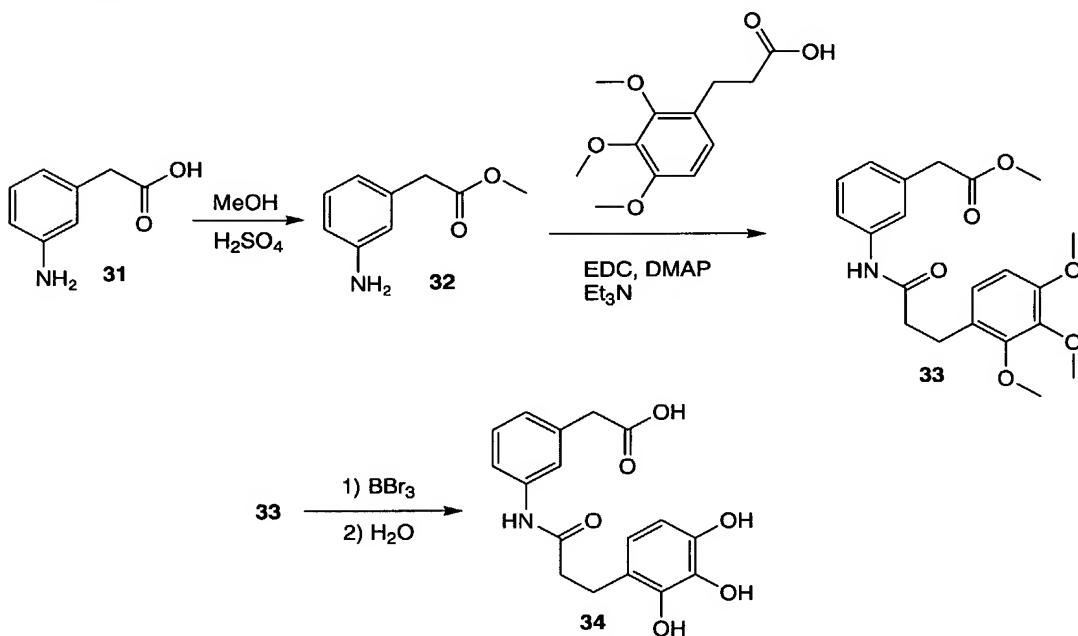
5

Step 1: Dissolve (3-Amino-phenyl)-acetic acid ((31),700mg, 4.63mmol) in MeOH (21mL) and add conc. sulfuric acid (0.27mL, 5.09mmol). Stir the reaction mixture for 2d under reflux. Cooled mixture to room temperature (rt), remove solvent under reduced

10 pressure and prepurify the residue by flushing it over a short pad of silica gel using EtOAc. Remove solvent again and partition the residue between EtOAc and saturated aqu. NaHCO$_3$ (1+1). Extracte the aqueous layer 3 times with EtOAc, washe the combined organic layers with brine and dried with Na$_2$SO$_4$. Remove solvent under reduced pressure and dry the residue without further purification in oil pump vacuum to obtain product (32)

15 as a light yellow oil (708mg, 92%). ^{1}H NMR (400MHz, CDCl$_3$): 3.51 (s, 2 H); 3.67 (s, 3 H); 6.57 (dd, 1 H, J_1 = 7.8Hz, J_2 = 1.8Hz); 6.60 (br.Ψt, 1 H, J = 1.8Hz); 6.65 (br.d, 1 H, J ≈ 7.8Hz); 7.08 (Ψt, 1 H, J = 7.8Hz).

Step 2: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve
EDC hydrochloride (187mg, 0.98mmol) and triethylamine (0.14mL, 1.00mmol) in
anhydrous dichloromethane (3.5mL) and stir for 5min at rt. Added 3-(2,3,4-Trimethoxy-
phenyl)-propionic acid (234mg, 0.97mmol) and DMAP (12mg, 0.10mmol) and stir for

5   10min. Add ester (32) (107mg, 0.65mmol) and stir the reaction solution overnight at rt.

Hydrolize the reaction solution with saturated aqu. NH$_4$Cl followed by water, separate
layers, extracte aqu. layer with dichloromethane (3 times) and washe the combined organic
layers with water and brine and dry with Na$_2$SO$_4$. Remove solvent under reduced pressure.

Purify crude product by preparative radial chromatography (silica gel 60PF, EtOAc/CyH

10   1+1) to obtain product (33) as a white solid (209mg, 83%). [K. C. Nicolaou; P. S. Baran;
Y.-L. Zhong; K. Sugita; *J. Am. Chem. Soc.;* **2002**; *124*; 10; 2212-2220]. ^{1}H NMR
(400MHz, CDCl$_3$): 2.62 (t, 2 H, *J* = 7.5Hz); 2.95 (t, 2 H, *J* = 7.5Hz); 3.58 (s, 2 H); 3.67 (s,
3 H); 3.82 (s, 3 H); 3.84 (s, 3 H); 3.91 (s, 3 H); 6.59 (d, 1 H, *J* = 8.6Hz); 6.86 (d, 1 H, *J* =
8.6Hz); 6.98 (br.d, 1 H, *J* = 7.8Hz); 7.32 (Ψt, 1 H, *J* = 7.8Hz); 7.38 (br.d, 1 H, *J* = 7.8Hz);

15   7.41 (br.s, 1 H).

Step 3: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve
(33) (139mg, 0.36) in anhydrous dichloromethane (1.8mL), cooled to –78°C (acetone/ dry
ice bath) and add slowly BBr$_3$ (0.51mL, 5.39mmol). Stir the reaction mixture for additional
30min at –78°C. Remove cooling bath and stir the reaction mixture for 3h at rt.

20   Cool reaction mixture to 0°C, add slowly water (0.50mL) under vigorous stirring followed
by dichloromethane (1.0mL) and methanol (2.0mL). Extract the mixture with EtOAc (3
times) and dry the combined organic layers with Na$_2$SO$_4$. Remove solvent under reduced
pressure and purify crude product by preparative RP HPLC (gradient, water/MeCN 95:5 to
5:95) to obtain {3-[3-(2,3,4-Trihydroxy-phenyl)-propionylamino]-phenyl}-acetic acid (34)

25   as a white solid (69mg, 57%). [T. P. Kogan; B. Dupré; H. Bui; K. L. McAbee; J. M.
Kassir; I. L. Scott; X. Hu; P. Vanderslice; P. J. Beck; R. A. F. Dixon *J. Med. Chem.;* **1998**;
41; 1099-1111]. ^{1}H NMR (400MHz, CD$_3$OD): 2.67 (t, 2 H, *J* = 7.6Hz); 2.92 (t, 2 H, *J* =
7.6Hz); 3.61 (s, 2 H); 6.31 (d, 1 H, *J* = 8.3Hz); 6.50 (d, 1 H, *J* = 8.3Hz); 7.05 (br.d, 1 H, *J*
= 7.8Hz); 7.28 (Ψt, 1 H, *J* = 7.8Hz); 7.48 (br.d, 1 H, *J* = 7.8Hz); 7.49 (br.s, 1 H).

30

EXAMPLE 2

(5-{2-[2-(2,3,4-Trihydroxyphenyl)-acetylamino]-phenyl}-thiophen-2-yl]acetic acid (41)

5

SCHEME 9
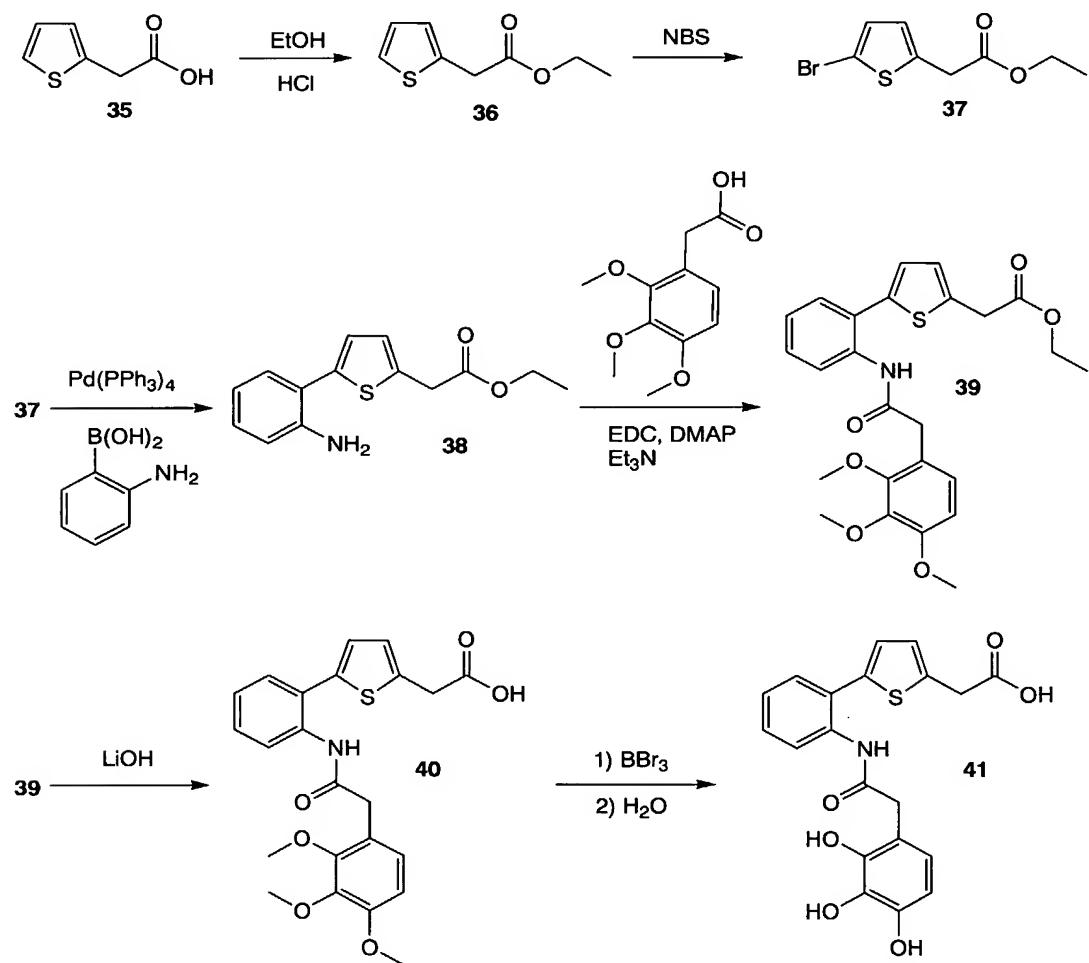
Step 1: Dissolve Thiophene-2-yl-acetic acid (35) (2.44g, 17.1mmol) in ethanol
(35mL) and add fuming aqu. hydrochloric acid (few drops). Stir the reaction mixture for
19h at 70 °C. Cool mixture to rt, remove solvent under reduced pressure and resolve the
residue in EtOAc. Wash this organic layer 3 times with 5% aqu. Na_2CO_3 and extract the
combined aqueous layer 3 times with EtOAc. Wash the combined organic layers with brine
and dry with Na_2SO_4. Remove solvent under reduced pressure and dry the residue without
further purification in oil pump vacuum to obtain product (36) as a light brown oil (2.78g,
95%). [J. Kunes; V. Balsanek; M. Pour; V. Buchta; *Collect. Czech. Chem. Commun.*,
2001, *66*; 12; 1809-1830]. ^{1}H NMR (400MHz, $CDCl_3$): 1.26 (t, 3 H, J = 7.1 Hz); 3.81 (s, 2
H); 4.17 (q, 2 H, J = 7.1 Hz); 6.91-6.96 (m, 2 H); 7.20 (d, 1H, J = 4.8 Hz).

Step 2: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve
ester (36) (1.30g, 7.64mmol) in anhydrous chloroform (6.0mL) and glacial acetic acid
(6.0mL), add N-Bromosuccinimide (1.39g, 7.79mmol) in portions and stir the mixture for
23h at rt. The mixture is diluted with an equal volume of water, the organic layer separated
and washed with a 1M aqu. NaOH, water, again with 1M aqu. NaOH and water (2 times).
Finally wash the organic layer with brine and dry with Na_2SO_4. Remove solvent under
reduced pressure. Purify crude product by preparative radial chromatography (silica gel
60PF, CyH/EtOAc 5+1] to obtain product (37) as an impured (according to NMR: 20%
sideproduct) orange liquid (1.61g, 85%) which is used without any further purification. [P.
M. Jackson; C.J. Moody; P. Sha; *J. Chem. Soc. Perkin Trans. 1*; **1990**; 2909-2918]. [1]H
NMR (400MHz, $CDCl_3$): 1.26 (t, 3 H, J = 7.1 Hz), 3.73 (s, 2 H); 4.17 (q, 2 H, J = 7.1 Hz);
6.67 (d, 1 H, J = 3.5 Hz); 6.88 (d, 1 H, J = 3.5 Hz).

Step 3: (The following reaction is done in an oxygenfree N_2 atmosphere.) Ethanol
(1.47mL), Tetrakis-(triphenylphosphine)-palladium(0) (59.0mg, 2.5mol%) and aqu.
Na_2CO_3 (1.60g, 5.60mmol; presolved in 2.0mL H_2O) are subsequently added to dissolved
2-Amino-benzeneboronic acid (341mg, 2.20 mmol) in toluene (16mL). The reaction
mixture is degassed 5 times and flooded with N_2 again. Add bromide (37) (498mg,
2.00mmol) and rinse with toluene (4.5 mL), degas again (5 times) and stir the reaction
solution 21h at 100°C. Partition the reaction solution between EtOAc and brine (1+1) and
extract the separated aqueous layer 3 times with EtOAc. Wash combined organic layer

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with brine and dry with Na$_2$SO$_4$. Remove solvent under reduced pressure and purify the crude product by preparative radial chromatography (silica gel 60PF, CyH/EtOAc 6+1, later 3+1] to obtain product (38) as a light yellow solid (300mg, 57%). [N. Miyaura; A. Suzuki; *Chem. Rev.*; 1995; 95; 2457]. ^{1}H NMR (400MHz, CDCl$_3$): 1.28 (t, 3 H, J = 7.1 Hz); 3.82 (s, 2 H); 4.19 (q, 2 H, J = 7.1 Hz); 6.77-6.84 (m, 2 H); 6.91 (d, 1 H, J = 3.5 Hz); 7.04 (d, 1 H, J = 3.5 Hz); 7.13 (td, 1 H, J = 7.8 Hz, 1.3 Hz); 7.25 (d, 1 H, J = 7.8 Hz).

Step 4: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Suspend EDC hydrochloride (86.3mg, 0.45mmol) in anhydrous dichloromethane (1.4mL), add triethylamine (0.063mL, 0.45mmol) and stir for 10min at rt. Add 2-(2,3,4-Trimethoxy-phenyl)-acetic acid (74.7mg, 0.33mmol) and DMAP (3.7mg, 0.03mmol) and stir for 15min. Added ester (38) (64,9mg, 0.30mmol) and stir the reaction solution 22h at rt. Partition the reaction solution between dichloromethane and water (1+1), separate layers and extract aqu. layer with dichloromethane (3 times). Wash the combined organic layer with brine and dry with Na$_2$SO$_4$. Purify crude product by preparative radial chromatography (silica gel 60PF, CyH/EtOAc 3+2) to obtain product (39) as yellow oil (118mg, 84%). ^{1}H NMR (400MHz, CDCl$_3$): 1.29 (t, 3 H, J = 7.1 Hz); 3.58 (s, 2 H); 3.74 (s, 3 H); 3.78 (s, 3 H); 3.79-3.80 (m, 2 H); 3.86 (s, 2 H); 4.20 (q, 2 H, J = 7.1 Hz); 6.58 (d, 1 H, J = 8.6 Hz); 6.59 (d, 1 H, J = 3.5 Hz); 6.75 (d, 1 H, J = 3.5 Hz); 6.85 (d, 1 H, J = 8.6 Hz); 7.05 (t, 1 H, J =7.8 Hz); 7.26 (dd, 1 H, J = 7.8 Hz, 1.3 Hz); 7.30 (td, 1 H, J = 7.8 Hz, 1.3 Hz); 7.90 (br.s; 1 H), 8.38 (d, 1 H, J = 8.3 Hz).

Step 5: Dissolve ester (39) (118mg, 0.25mmol) in methanol (8.0mL), add a 1M aqu. LiOH solution (1.76mL, 1.76mmol) and stir 20h at rt. Remove solvent under reduced pressure und partition residue between CHCl$_3$ and 0.5M HCl (1+1). Separate the aqueous layer and extract 3 times with CHCl$_3$. Wash the combined organic layer with brine and dry with Na$_2$SO$_4$. Remove solvent under reduced pressure and dry the residue without further purification in oil pump vacuum to obtain crude product (40) as light brown foam (120mg, quant.). ^{1}H NMR (400MHz, CDCl$_3$): 3.58 (s, 2 H); 3.73 (s, 3 H); 3.78 (s, 3 H); 3.85 (s, 2 H); 3.86 (s, 3 H); 6.58-6.61 (m, 1 H); 6.59 (d, 1 H, J = 8.3 Hz); 6.77 (d, 1 H, J = 3.5 Hz); 6.86 (d, 1 H, J = 8.3 Hz); 7.06 (t, 1 H, J = 7.8 Hz); 7.22-7.27 (m, 1 H); 7.31 (td, 1 H, J = 7.8 Hz, 1.3 Hz); 7.86 (br.s, 1 H); 8.37 (d, 1 H, J = 8.3 Hz).

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Step 6: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve
(40) (118mg, 0.27mmol) in anhydrous dichloromethane (2.5mL), cool to −78°C (acetone/
dry ice) and add slowly a 1M BBr$_3$ solution in dichloromethane (1.61mL, 1.61mmol). Stir
the reaction mixture for additional 30min at −78°C. Remove cooling bath and stir the
reaction mixture for 4h at rt. Cool reaction mixture to 0°C, add slowly water (1.00mL)
under vigorous stirring. Partition the reaction mixture between EtOAc and water (1+1).
Extract the separated aqueous layer with EtOAc (2 times) and wash the combined organic
layer with brine and dry with Na$_2$SO$_4$. Remove solvent under reduced pressure and purify
crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain (5-
{2-[2-(2,3,4-Trihydroxyphenyl)-acetylamino]-phenyl}-thiophen-2-yl]acetic acid (41) as a
light brown foam (53mg, 50%). ^{1}H NMR (400MHz, CDCl$_3$): 3.54 (s, 2 H); 3.82 (s, 2 H);
6.34 (d, 1 H, J = 8.3 Hz); 6.49 (d, 1 H, J = 8.3 Hz); 6.76 (d, 1 H, J = 3.3 HZ); 6.81 (d, 1 H,
J = 3.3 Hz); 7.18 (t, 1 H, J = 7.6 Hz); 7.32 (t, 1 H, J = 7.8 Hz); 7.39 (d, 1 H, J = 7.3 Hz);
7.90 (d, 1 H, J = 8.1 Hz); 8.20 (br.s, 1 H).

EXAMPLE 3

**(5-{2-[(2',3',4'-Trihydroxy-biphenyl-3-carbonyl)-amino]-phenyl}-thiophen-2-yl)-
acetic acid (48)**

and

**(5-{2-[(2',3',4'-Trihydroxy-biphenyl-3-carbonyl)-amino]-phenyl}-thiophen-2-yl)-
acetic acid methyl ester (49)**

SCHEME 10
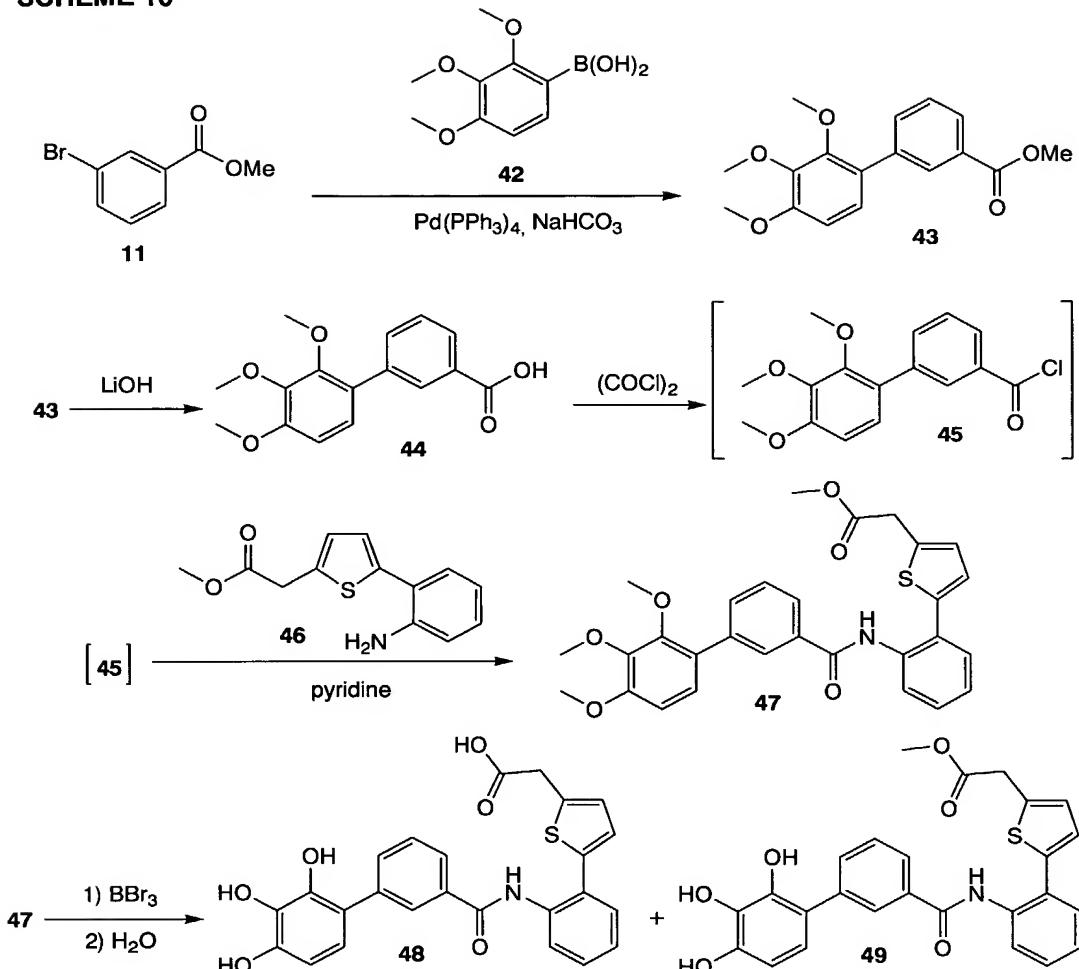
Step 1: (The following reaction is done in an N_2 atmosphere.) To a solution of
2,3,4-Trimethoxyphenylboronic acid (42) (1.40g, 6.60mmol) in toluene (15.0mL) is added
EtOH (2.0mL), Pd(PPh$_3$)$_4$ (208mg, 0.18mmol) and Na$_2$CO$_3$·10H$_2$O (4.81g, 16.80mmol) in
water (5.2mL). The resulting mixture is carefully degassed (5 times alternating vacuum
and flushing with N_2). A solution of Methyl-3-bromobenzoate (11) (1.29g, 6.00mmol) in
toluene (9.0mL) is added by syringe, the resulting mixture is again carefully degassed and
stirred overnight at 100°C. Partition the mixture between brine/EtOAc (1+1), separate
layers, extract the aqu. layer with EtOAc (3x), wash the combined organic layer with brine,
dry with Na$_2$SO$_4$ and remove solvent. Purify crude product by preparative radial
chromatography (silica gel, EtOAc/CyH 1+5) to obtain 2',3',4'-Trimethoxy-biphenyl-3-
carboxylic acid methyl ester (43) as a yellowish oil (1.07g, 58%). ^{1}H NMR (400MHz,

CDCl$_3$): 3.66 (s, 3 H); 3.89 (s, 3 H); 3.92 (s, 6 H); 6.74 (d, 1 H, J = 8.6Hz); 7.03 (d, 1 H, J = 8.6Hz); 7.44 (t, 1 H, J = 7.8Hz); 7.70 (d, 1 H, J = 7.6Hz); 7.97 (d, 1 H, J = 7.8Hz); 8.15 (br.s 1 H).

Step 2: Dissolve 2',3',4'-Trimethoxy-biphenyl-3-carboxylic acid methyl ester (43) (566mg, 1.87mmol) in MeCN (19.0mL) at rt and add 1M aqu LiOH (9.36mL, 9.36mmol). Stir reaction mixture overnight at rt. Quench reaction mixture (cooling bath) with 1M aqu. HCl (to get pH ca. 3). Extract the mixture with EtOAc (3x), wash the combined organic layer with brine and dry with Na$_2$SO$_4$. Recrystallize crude product from EtOAc/CyH 1+3 to obtain 2',3',4'-Trimethoxy-biphenyl-3-carboxylic acid (44) as a white solid (392mg, 72%). ^{1}H NMR (400MHz, CD$_3$OD: 3.68 (s, 3 H); 3.93 (br.s, 6 H); 6.92 (d, 1 H, J = 8.6Hz); 7.11 (d, 1 H, J = 8.6Hz); 7.54 (t, 1 H, J = 7.7Hz); 7.75 (d, 1 H, J = 7.6Hz); 8.01 (d, 1 H, J = 7.8Hz); 8.18 (br.s 1 H).

Step 3: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve 2',3',4'-Trimethoxy-biphenyl-3-carboxylic acid (44) (107mg, 0.37mmol) in anhydrous DCM (3.0mL) and add anhydrous DMF (3 drops, cat. amount). Then add slowly oxalyl chloride (42μL, 0.48mmol) by keeping temperature at ca. 15°C with a water bath and stir the turbid mixture for additional 2h at rt. Transfer the formed crude solution of 2',3',4'-Trimethoxy-biphenyl-3-carbonyl chloride (45) to an ice cooled solution of [5-(2-Amino-phenyl)-thiophen-2-yl]-acetic acid methyl ester (46) (70mg, 0.28mmol) in anhydrous DCM (4.5mL) and anhydrous pyridine (0.75mL). Stir the reaction mixture for 3h at rt. Pour the reaction mixture into ice cooled 1M aqu. HCl, extract with DCM (3x), wash the combined organic layer with brine and dry with Na$_2$SO$_4$. Purify the crude product by preparative radial chromatography (silica gel, EtOAc/CyH 1+3, later 1+2) to obtain (5-{2-[(2',3',4'-Trimethoxy-biphenyl-3-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic acid methyl ester (47) as a brownish sticky solid (96mg, 65%). ^{1}H NMR (400MHz, CDCl$_3$): 3.64 (s, 3 H); 3.71 (s, 3 H); 3.84 (s, 2 H); 3.90 (s, 3 H); 3.92 (s, 3 H); 6.75 (d, 1 H, J = 8.8Hz); 6.97 (d, 1 H, J = 3.5Hz); 7.01 (d, 1 H, J = 8.8Hz); 7.03 (d, 1 H, J = 3.5Hz); 7.16 (br.t, 1 H, J = 7.6Hz); 7.36-7.43 (m, 2 H); 7.46 (t, 1 H, J = 7.7Hz); 7.67 (Ψdd, 2 H, J_1 = 7.6Hz, J_2 = 1.5Hz); 7.91 (br.s 1 H); 8.41 (br.s 1 H); 8.50 (d, 1 H, J = 8.6Hz).

Step 4: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve (5-{2-[(2',3',4'-Trimethoxy-biphenyl-3-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic

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acid methyl ester (47) (66mg, 0.13mmol) in anhydrous DCM (3.4mL) at −78°C, add

dropwise a 1M solution of BBr₃ in DCM (1.05mL, 1.05mmol) and stir for additional

30min at −78°C. After slowly warming up stir the reaction solution for additional 4h at rt.

Cool reaction mixture to 0°C, add dropwise water and DCM under vigorous stirring

5   followed by MeOH to homogenize the mixture. Partition the hydrolized reaction mixture

between water and EtOAc, extract the aqu. layer with EtOAc (3x), wash combined organic

layer with brine and dry it with Na₂SO₄. Purify the crude product by preparative RP HPLC

(gradient, water/CH₃CN 95:5 to 5:95) to obtain (5-{2-[(2',3',4'-Trihydroxy-biphenyl-3-

carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic acid (48) (8mg, 13%) as a white solid and

10   (5-{2-[(2',3',4'-Trihydroxy-biphenyl-3-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic

acid methyl ester (49) (14mg, 23%) as a brown foam. ¹H NMR (400MHz, CD₃OD) (48):

3.86 (s, 2 H); 6.49 (d, 1 H, J = 8.6Hz); 6.74 (d, 1 H, J = 8.6Hz); 6.98 (d, 1 H, J = 3.0Hz);

7.19 (d, 1 H, J = 3.3Hz); 7.36 (t, 1 H, J = 7.6Hz); 7.43 (t, 1 H, J = 7.6Hz); 7.51 (t, 1 H, J =

7.8Hz); 7.62 (d, 1 H, J = 7.8Hz); 7.71-7.84 (m, 3 Hz); 8.08 (br.s 1 H); (49): 3.66 (s, 3 H);

15   3.88 (s, 2 H); 6.49 (d, 1 H, J = 8.3Hz); 6.74 (d, 1 H, J = 8.3Hz); 6.97 (d, 1 H, J = 3.5Hz);

7.19 (d, 1 H, J = 3.5Hz); 7.36 (td, 1 H, J_1 = 7.6Hz, J_2 = 1.5Hz); 7.43 (td, 1 H, J_1 = 7.6Hz,

J_2 = 1.5Hz); 7.51 (t, 1 H, J = 7.8Hz); 7.62 (dd, 1 H, J_1 = 7.6Hz, J_2 = 1.5Hz); 7.73 (d, 1 H, J

= 7.8Hz); 7.81 (Ψdd, 2 H, J_1 = 7.6Hz, J_2 = 1.5Hz); 8.09 (br.s 1 H).

EXAMPLE 4

20

4-Methyl-3-[3-(2,3,4-trihydroxy-phenyl)-acryloylamino]-benzoic acid (54)
and
4-Methyl-3-[3-(2,3,4-trihydroxy-phenyl)-acryloylamino]-benzoic acid methyl
ester (55)

25

SCHEME 11
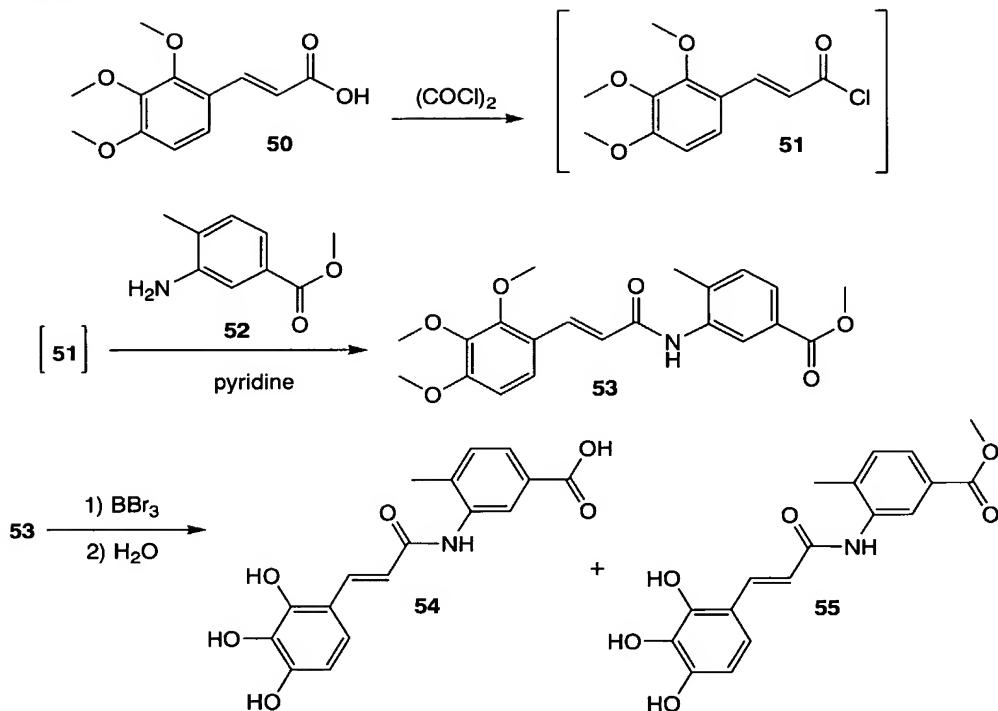
Step 1: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve trans-2,3,4-Trimethoxycinnamic acid (50) (200mg, 0.84mmol) in anhydrous DCM (4.4mL) at rt and add anhydrous DMF (3 drops, cat. amount). Then add slowly oxalyl chloride (96μL, 1.09mmol) stir the turbid mixture for additional 2h at rt. Remove solvent and dry the residue in oil pump vacuum to obtain trans-2,3,4-Trimethoxycinnamic acid chloride (51) (ca.0.84mmol) as an yellow solid. Dissolve acid chloride (51) (108mg, 0.42mmol) in anhydrous DCM (4.0mL) and add it to an ice cooled solution of Methyl 3-amino-4-methylbenzoate (52) (69mg, 0.42mmol) in anhydrous DCM (2.0mL) and anhydrous pyridine (1.2mL). Stir the resulting reaction mixture at rt overnight. Pour the reaction mixture into ice cooled 1M aqu. HCl, extract with EtOAc (3x), wash the combined organic layer with brine and dry it with Na_2SO_4. Purify the crude product by filtration through a short pad of silica gel with EtOAc and remove solvent to obtain 4-Methyl-3-[3-(2,3,4-trimethoxy-phenyl)-acryloylamino]-benzoic acid methyl ester (53) (99mg, 61%) as a light yellow solid. ^{1}H NMR (400MHz, CDCl$_3$): 2.35 (s, 3 H); 3.87 (s, 3 H); 3.88 (s, 6 H); 3.91 (br.s, 3 H); 6.59 (d, 1 H, J = 15.6Hz); 6.68 (d, 1 H, J = 8.6Hz); 7.08

(br.s, 1 H); 7.20-7.29 (m, 2 H); 7.77 (br.d, 1 H, J = 8.6Hz); 7.90 (d, 1 H, J = 15.6Hz); 8.55 (br.s 1 H).

    Step 2: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve anilide (53) (40mg, 0.10mmol) in anhydrous DCM (1.3mL) at –78°C, add dropwise a 1M solution of BBr_3 in DCM (830μL, 0.83mmol) and stir for additional 30min at –78°C. After slowly warming up stir the reaction solution for additional 4h at rt. Cool reaction mixture to 0°C, add dropwise water and DCM under vigorous stirring followed by MeOH to homogenize the mixture. Partition the hydrolized reaction mixture between water and EtOAc, extract the aqu. layer with EtOAc (3x), wash combined organic layer with brine and dry it with Na_2SO_4. Purify the crude product by preparative RP HPLC (gradient, water/CH_3CN 95:5 to 5:95) to obtain 4-Methyl-3-[3-(2,3,4-trihydroxy-phenyl)-acryloylamino]-benzoic acid (54) (6.5mg, 19%) as an yellowish solid and 4-Methyl-3-[3-(2,3,4-trihydroxy-phenyl)-acryloylamino]-benzoic acid methyl ester (55) (9mg, 25%) as an yellowish solid. ^{1}H NMR (400MHz, CD_3OD) (54): 2.40 (s, 3 H); 6.43 (d, 1 H, J = 8.6Hz); 6.90 (d, 1 H, J = 15.6Hz); 6.97 (d, 1 H, J = 8.6Hz); 7.40 (d, 1 H, J = 8.1Hz); 7.83 (dd, 1 H, J_1 = 8.1Hz, J_2 = 1.5Hz); 7.93 (d, 1 H, J = 15.6Hz); 8.17 (br.s, 1 H); (55): 2.40 (s, 3 H); 3.93 (s, 3 H); 6.43 (d, 1 H, J = 8.6Hz); 6.90 (d, 1 H, J = 15.7Hz); 6.97 (d, 1 H, J = 8.6Hz); 7.40 (d, 1 H, J = 8.1Hz); 7.82 (dd, 1 H, J_1 = 7.8Hz, J_2 = 1.7Hz); 7.93 (d, 1 H, J = 15.9Hz); 8.18 (br.s, 1 H).

EXAMPLE 5

5-{2-Amino-4-[2-(3,4,5-trihydroxy-phenyl)-acetylamino]-phenyl}-2-methyl-furan-3-carboxylic acid (62)

SCHEME 12
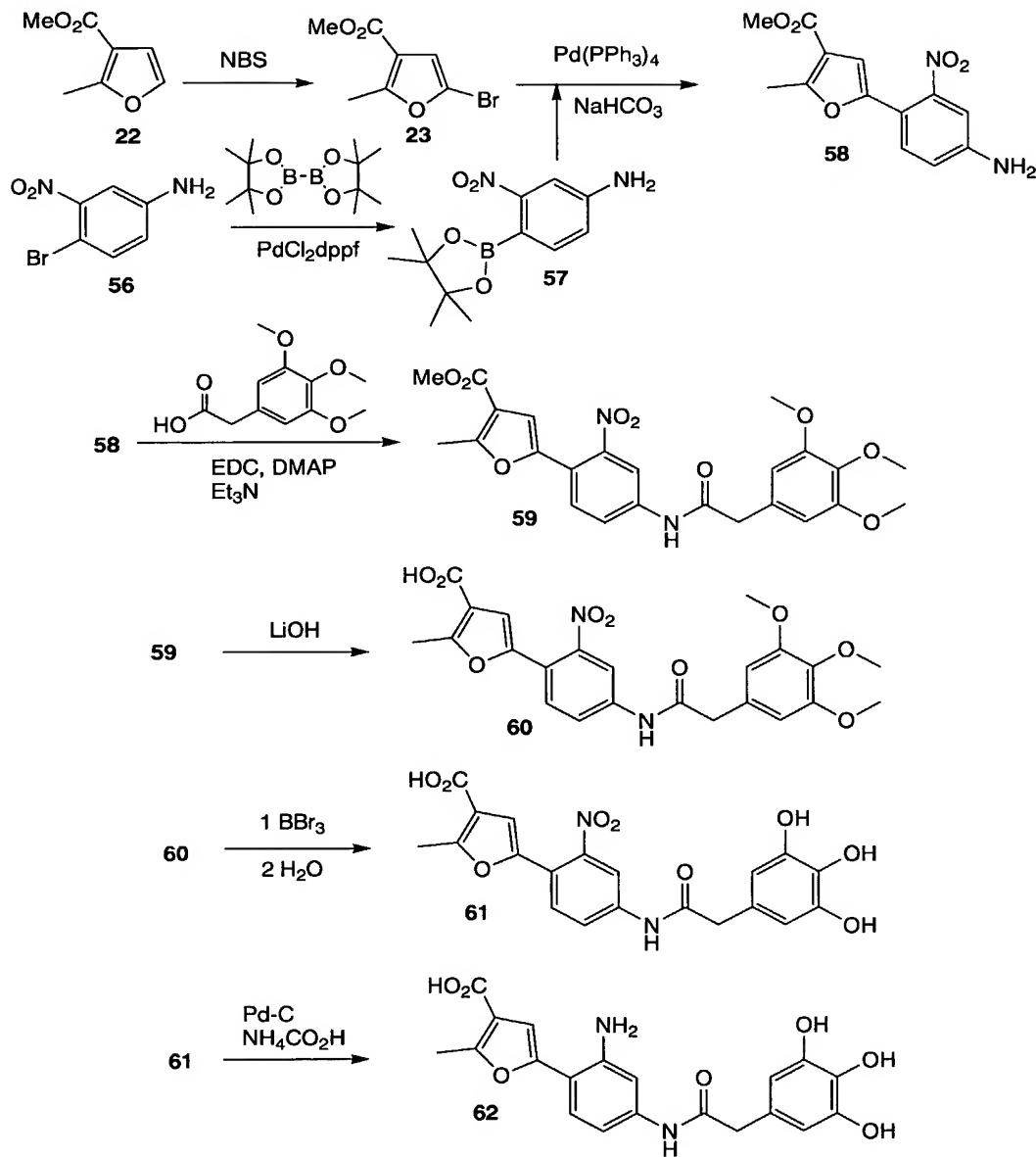
Step 1: (The following reaction is done under exclusion of light.) Dissolve 2-
Methyl-furan-3-carboxylic acid methyl ester (22) (2.00mL, 15.9mmol) in chloroform
(11mL) and glacial acetic acid (11mL) and add NBS (3.85g, 21.6mmol) portionwise in
between a period of 75min. Stir the reaction suspension for additional 16h at rt. Add water
to the reaction mixture and extract the aqu. layer with DCM (2 times), wash the combined
organic layer with 2M aqu. NaOH, water and brine and dry it with Na_2SO_4 to obtain 5-

Bromo-2-methyl-furan-3-carboxylic acid methyl ester (23) (2.80g, 80%) as a red brown oil. No further purification. ^{1}H NMR (400MHz, CDCl$_3$): 2.54 (s, 3 H); 3.80 (s, 3 H); 6.53 (s, 1 H).

Step 2: (The following reaction is done in a N$_2$ atmosphere.) Dissolve

5   PdCl$_2$(dppf)˙CH$_2$Cl$_2$ (245mg, 0.30mmol), KOAc (2.52g, 25.7mmol) and Bis-(pinacolato)diboron (3.81g, 15.00mmol) in anhydrous DMSO (50mL) and add 4-Bromo-3-nitro-phenylamine (56) (2.17g, 10.00mmol). Degas the mixture carefully and flush with N$_2$ again (5 times) and stir it for 24h at 80°C. Cool the reaction mixture to rt and partition it between water and toluene. Extract the aqu. layer with EtOAc (3 times), wash the

10   combined organic layer with water and brine and dry it with Na$_2$SO$_4$. The obtained crude residue is filtrated through a short pad of silica gel using EtOAc/CyH (1+1) to obtain 3-Nitro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (57) (2.04g, 77%) as a dark red solid. No further purification. ^{1}H NMR (400MHz, CDCl$_3$): 1.37 (s, 12 H); 3.95 (br.s, 2 H); 6.87 (dd, 1 H, J_1 = 7.8Hz, J_2 = 2.3Hz); 7.30 (d, 1 H, J = 8.1Hz); 7.35 (d, 1 H, J

15   = 2.3Hz).

Step 3: (The following reaction is done in a N$_2$ atmosphere.) Dissolve Pd(PPh$_3$)$_4$ (59mg, 0.05mmol) and 5-Bromo-2-methyl-furan-3-carboxylic acid methyl ester (23) (447mg, 2.04mmol) in DME (3mL) and stir for 10min at rt. Add 3-Nitro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (57) (465mg, 1.76mmol) followed by

20   an aqu. 1M sodium bicarbonate solution (5.10mL, 5.10mmol). Degas the reaction mixture carefully, flush with N$_2$ (5 times) and stir for 4,5h at 90°C (reflux). Cool reaction mixture to rt, remove organic solvent under reduced pressure and partition the residue between water and EtOAc. Extract the aqu. layer with EtOAc (3 times), wash the combined organic layer with water and brine and dry it with Na$_2$SO$_4$. Purify the obtained crude product by

25   flash chromatography (silica gel, EtOAc/CyH 1+3, later 1+2) to obtain 5-(4-Amino-2-nitro-phenyl)-2-methyl-furan-3-carboxylic acid methyl ester (58) (167mg, 34%) as a red solid. ^{1}H NMR (400MHz, CDCl$_3$): 2.57 (s, 3 H); 3.81 (s, 3 H); 4.05 (br.s, 2 H); 6.68 (s, 1 H); 6.81 (dd, 1 H, J_1 = 8.3Hz, J_2 = 2.3Hz); 6.99 (d, 1 H, J = 2.3Hz); 7.39 (d, 1 H, J = 8.3Hz).

30   **Step 4:** (The following reaction is done in an anhydrous N$_2$ atmosphere.) Suspend EDC˙HCl (138mg, 0.72mmol) and Et$_3$N (101μL, 0.72) in anhydrous DCM (4.5mL) and stir

the resulting solution for 5min at rt. Add 2-(3,4,5-Trimethoxy-phenyl)-acetic acid (163mg, 0.72mmol) and DMAP (8mg, 0.07mmol) and stir the resulting solution for 10min. Add 5-(4-Amino-2-nitro-phenyl)-2-methyl-furan-3-carboxylic acid methyl ester (58) (100mg, 0.36mmol) and stir the reaction solution for 22h at rt. Quench reaction solution with sat.

5   aqu. NH$_4$Cl and water, separate layers and extract aqu. layer with DCM (3 times). Wash the combined organic layer with water and brine and dry with Na$_2$SO$_4$. Purify the crude product by preparative radial chromatography (silica gel, EtOAc/CyH 1+1) to obtain 2-Methyl-5-{2-nitro-4-[2-(3,4,5-trimethoxy-phenyl)-acetylamino]-phenyl}-furan-3-carboxylic acid methyl ester (59) (96mg, 55%) as an yellow solid. ^{1}H NMR (400MHz,

10   CDCl$_3$): 2.55 (s, 3 H); 3.65 (s, 2 H); 3.79 (s, 3 H); 3.81 (s, 6 H); 3.82 (s, 3 H); 6.50 (s, 2 H); 6.77 (s, 1 H); 7.53 (d, 1 H, J = 8.6Hz); 7.66 (dd, 1 H, J_1 = 8.6Hz, J_2 = 2.0Hz); 7.93 (br.s, 1 H); 7.96 (d, 1 H, J = 2.0Hz).

Step 5: Dissolve 2-Methyl-5-{2-nitro-4-[2-(3,4,5-trimethoxy-phenyl)-acetylamino]-phenyl}-furan-3-carboxylic acid methyl ester (59) (50mg, 0.10mmol) in THF

15   (1.0mL) and MeOH (0.5mL) at rt and add 1M aqu LiOH (525μL, 0.52mmol). Stir the reaction mixture for 17h at rt. Add dropwise 1M aqu. HCl (580μL, 0.58mmol) and extract the mixture with EtOAc (3 times), wash the combined organic layer with brine and dry it with Na$_2$SO$_4$. Purify the obtained crude product by preparative TLC (silica gel, EtOAc/MeOH 9+1) to obtain 2-Methyl-5-{2-nitro-4-[2-(3,4,5-trimethoxy-phenyl)-acetylamino]-phenyl}-furan-3-carboxylic acid (60) (35mg, 71%) as a brown sticky solid.

20   acetylamino]-phenyl}-furan-3-carboxylic acid (60) (35mg, 71%) as a brown sticky solid. ^{1}H NMR (400MHz, CDCl$_3$): 2.61 (s, 3 H); 3.70 (s, 2 H); 3.86 (s, 3 H); 3.87 (s, 6 H); 6.51 (s, 2 H); 6.85 (s, 1 H); 7.29 (br.s, 1 H); 7.58 (d, 1 H, J = 8.6Hz); 7.62 (dd, 1 H, J_1 = 9.0Hz, J_2 = 2.2Hz); 7.98 (d, 1 H, J = 2.0Hz).

Step 6: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve

25   2-Methyl-5-{2-nitro-4-[2-(3,4,5-trimethoxy-phenyl)-acetylamino]-phenyl}-furan-3-carboxylic acid (60) (33mg, 0.07mmol) in anhydrous DCM (1.0mL), cool the solution to −78°C and add dropwise BBr$_3$ (66μL, 0.70mmol). Stir the reaction mixture for 10min at −78°C and after slowly warming up for additional 2h at rt. Cool reaction mixture to 0°C, add dropwise water and DCM followed by MeOH to homogenize the mixture and remove

30   solvent. Suspend the crude product in MeOH and filtrate it through a short pad of celite to obtain 2-Methyl-5-{2-nitro-4-[2-(3,4,5-trihydroxy-phenyl)-acetylamino]-phenyl}-furan-3-

carboxylic acid (61) (22mg, 72%) as a brown solid. ^{1}H NMR (400MHz, CD$_3$OD): 2.62 (s, 3 H); 3.53 (s, 2 H); 6.40 (s, 2 H); 6.88 (s, 1 H); 7.73 (d, 1 H, J = 8.6Hz); 7.80 (dd, 1 H, J_1 = 8.6Hz, J_2 = 2.0Hz); 8.24 (d, 1 H, J = 2.0Hz).

Step 7: (The following reaction is done in an N$_2$ atmosphere.) Dissolve 2-Methyl-5-{2-nitro-4-[2-(3,4,5-trihydroxy-phenyl)-acetylamino]-phenyl}-furan-3-carboxylic acid (61) (21mg, 0.05mmol) in MeOH (1.5mL) and add Pd on carbon (10% (w/w) Pd content, 11.5mg, 0.005mmol) followed by NH$_4$CO$_2$H (68mg, 1.08mmol) at rt. Degas the reaction mixture carefully (flush with N$_2$) and stir it for 17h at rt. Filtrate reaction mixture through a short pad of celite and remove solvent. Purify the crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain 5-{2-Amino-4-[2-(3,4,5-trihydroxy-phenyl)-acetylamino]-phenyl}-2-methyl-furan-3-carboxylic acid (62) (4.6mg, 23%) as a white solid. ^{1}H NMR (400MHz, CD$_3$OD): 2.69 (s, 3 H); 3.50 (s, 2 H); 6.39 (s, 2 H); 6.91 (s, 1 H); 7.13 (br.d, 1 H, J = 8.6Hz); 7.57 (d, 1 H, J = 8.6Hz) 7.65 (br.s, 1 H).

EXAMPLE 6

{4-[2-(3,4,5-Trihydroxy-phenyl)-acetyl]-piperazin-1-yl}-acetic acid ethyl ester (65)

SCHEME 13
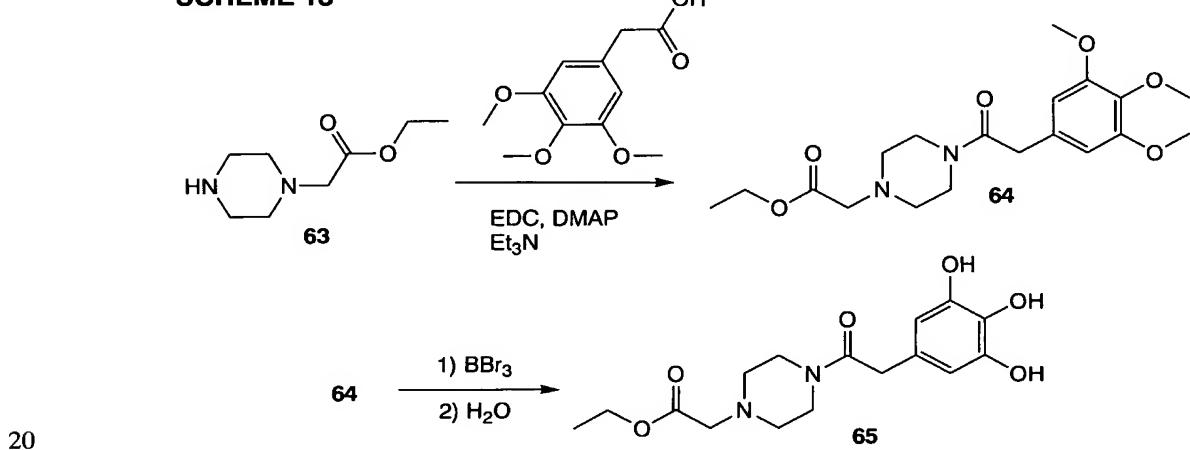
Step 1: (The following reaction is done in an anhydrous N_2 atmosphere.) Suspend EDC·HCl (188mg, 0.98mmol) and Et_3N (137μL, 0.98mmol) in anhydrous DCM (1.0mL) and stir the resulting solution for 5min at rt. Add 2-(3,4,5-Trimethoxy-phenyl)-acetic acid (163mg, 0.72mmol) and DMAP (8mg, 0.07mmol) and stir the resulting solution for 10min.

5 Add 1-(Ethoxycarbonylmethyl)piperazine (63) (112mg, 0.65mmol) and stir the reaction solution overnight at rt. Quench reaction solution with sat. aqu. NH_4Cl and water, separate layers and extract aqu. layer with DCM (3 times). Wash the combined organic layer with water and brine and dry with Na_2SO_4. Purify the crude product by preparative radial chromatography (silica gel, EtOAc/MeOH 10+1) to obtain {4-[2-(3,4,5-Trimethoxy-

10 phenyl)-acetyl]-piperazin-1-yl}-acetic acid ethyl ester (64) (99mg, 40%) as a colorless oil.
^{1}H NMR (400MHz, $CDCl_3$): 1.25 (t, 3 H, J = 7.1Hz); 2.48 (br.m, 2 H); 2.58 (br.m, 2 H); 3.21 (br.s, 2 H); 3.53 (br.m, 2 H); 3.65 (s, 2 H); 3.71 (br.m, 2 H); 3.81 (s, 3 H); 3.82 (s, 6 H); 4.16 (q, 2 H, J = 7.1Hz); 6.42 (s, 2 H).

Step 2: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve

15 {4-[2-(3,4,5-Trimethoxy-phenyl)-acetyl]-piperazin-1-yl}-acetic acid ethyl ester (64) (99mg, 0.26mmol) in anhydrous DCM (6.0mL), cool the solution to $-78°$C and add dropwise a 1 M BBr_3 solution in DCM (2.30mL, 2.30mmol). Stir the reaction mixture for 30min at $-78°$C and after slowly warming up for additional 4h at $-20°$C. Add dropwise water and extract the mixture with EtOAc (3 times). Wash the combined organic layer with

20 brine and dry it dry with Na_2SO_4. Purify the crude product by preparative RP HPLC (gradient, water/CH_3CN 95:5 to 5:95) to obtain {4-[2-(3,4,5-Trihydroxy-phenyl)-acetyl]-piperazin-1-yl}-acetic acid ethyl ester (65) (34mg, 40%) as a sticky brownish solid.
^{1}H NMR (400MHz, CD_3OD): 1.35 (t, 3 H, J = 7.1Hz); 3.14-3.24 (br.m, 2 H); ca. 3.32 (br.m, 2 H); 3.65 (s, 2 H); 3.78-4.00 (br.m, 4 H); 4.12 (s, 2 H); 4.34 (q, 2 H, J = 7.1Hz);

25 6.29 (s, 2 H).

EXAMPLE 7

{4-[3-(3,4,5-Trihydroxy-phenyl)-propionyl]-piperazin-1-yl}-acetic acid (68)

30

SCHEME 14
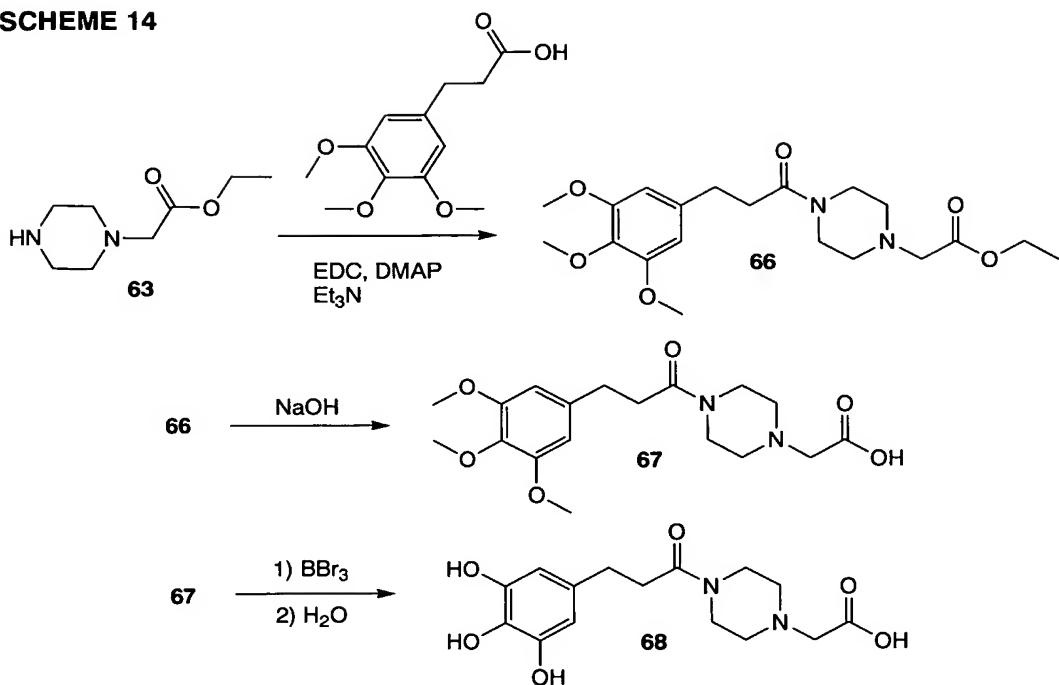
Step 1: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Suspend EDC·HCl (376mg, 1.96mmol) and Et$_3$N (275μL, 1.96mmol) in anhydrous DCM (2.0mL) and stir the resulting solution for 5min at rt. Add 3-(3,4,5-Trimethoxy-phenyl)-propionic acid (346mg, 1.44mmol) and DMAP (17mg, 0.14mmol) and stir the resulting solution for 15min. Add 1-(Ethoxycarbonylmethyl)piperazine (63) (224mg, 1.30mmol) and stir the reaction solution overnight at rt. Quench reaction solution with water, separate layers and extract aqu. layer with EtOAc (3 times). Filtrate the combined organic layer through a short pad of silica gel and remove solvent. Purify the crude product by preparative radial chromatography (silica gel, EtOAc/MeOH 9+1) to obtain {4-[3-(3,4,5-Trimethoxy-phenyl)-propionyl]-piperazin-1-yl}-acetic acid ethyl ester (66) (426mg, 83%) as a colorless oil. ^{1}H NMR (400MHz, CDCl$_3$): 1.26 (t, 3 H, J = 7.1Hz); 2.45-2.70 (br.m, 6 H); 2.89 (t, 2 H, J = 7.7Hz); 3.26 (br.s, 2 H); 3.43-3.56 (br.m, 2 H); 3.61-3.76 (br.m, 2 H); 3.80 (s, 3 H); 3.83 (s, 6 H); 4.18 (q, 2 H, J = 7.1Hz); 6.41 (s, 2 H).

Step 2: Dissolve {4-[3-(3,4,5-Trimethoxy-phenyl)-propionyl]-piperazin-1-yl}-acetic acid ethyl ester (66) (100mg, 0.25mmol) in MeOH (2.0mL) at rt and add 2M aqu NaOH (260μL, 0.52mmol). Stir the reaction mixture for 1h under reflux. Add dropwise 1M aqu. HCl (550μL, 0.55mmol), extract the mixture with EtOAc (3 times) and remove

solvent obtain {4-[3-(3,4,5-Trimethoxy-phenyl)-propionyl]-piperazin-1-yl}-acetic acid
(67) (88mg, 95%) as a brown sticky solid. No further purification. ^{1}H NMR (400MHz,
CDCl$_3$/CD$_3$OD 9+1): 2.54 (br.t, 2 H); 2.78 (t, 2 H, J = 7.5Hz); 2.83-3.10 (br.m, 2 H); 3.24
(s, 2 H); 3.43-3.62 (br.m, 2 H); 3.68 (s, 3 H); 3.73 (s, 6 H); 3.74-3.85 (br.m, 4 H); 6.34 (s, 2
H).

Step 3: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve
{4-[3-(3,4,5-Trimethoxy-phenyl)-propionyl]-piperazin-1-yl}-acetic acid (67) (88mg,
0.24mmol) in anhydrous DCM (10mL), cool the solution to −78°C and add dropwise BBr$_3$
(330μL, 3.50mmol). Stir the reaction mixture for 30min at −78°C and after slowly
warming up for additional 4h at −20°C. Add dropwise water and remove solvent. Purify
the crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain
{4-[3-(3,4,5-Trimethoxy-phenyl)-propionyl]-piperazin-1-yl}-acetic acid (68) (2mg, 2%) as
a white solid. ^{1}H NMR (400MHz, CD$_3$OD): 2.67 (t, 2 H, J = 6.9Hz); 2.79 (t, 2 H, J =
6.9Hz); 2.86-2.96 (br.m, 2 H); 3.23-3.31 (br.m, 2 H); 3.67-3.77 (br.m, 2 H); 3.80-3.93
(br.m, 2 H); 3.95 (s, 2 H); 6.25 (s, 2 H).

EXAMPLE 8

**{2'-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-biphenyl-3-yl}-acetic acid
methyl ester (73)**

SCHEME 15
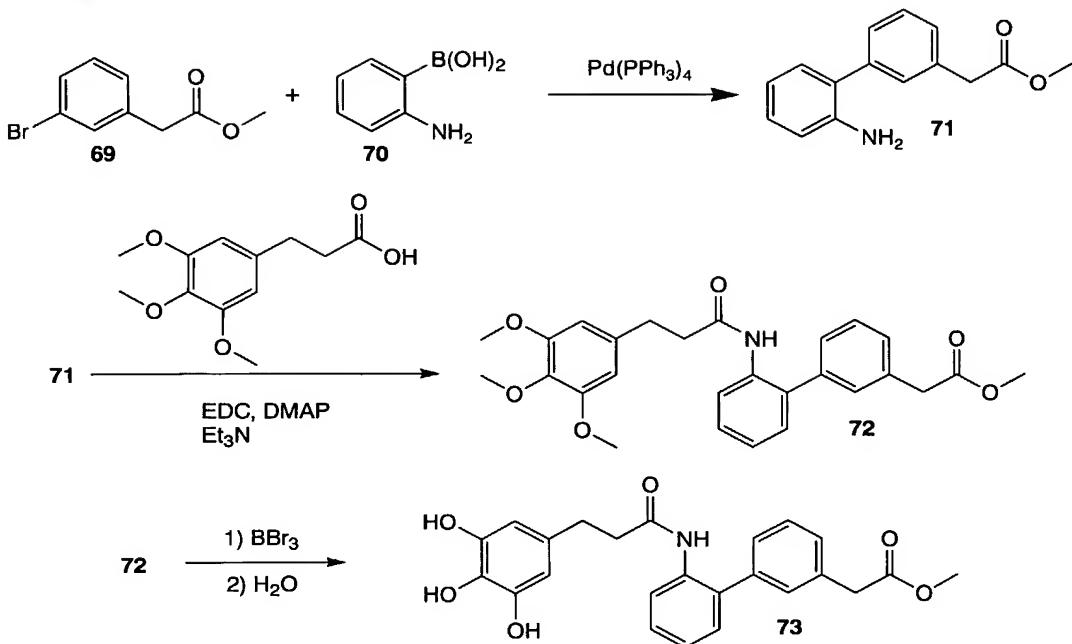
Step1: (The following reaction is done in an oxygenfree N_2 atmosphere.) Add ethanol (0.8mL), Tetrakis-(triphenylphosphine)-palladium(0) (30mg, 2.2mol%) and Na$_2$CO$_3$ decahydrate (944mg, 3.30mmol; presolved in 1.2mL H_2O) subsequently to dissolved 2-Amino-benzeneboronic acid (70) (201mg, 1.30 mmol) in toluene (6.0mL). Degas the reaction mixture for 5 times and flood with N_2 again. Add (3-Bromo-phenyl)-acetic acid methyl ester (69) (270mg, 1.18mmol) in toluene (6.0 mL), degas again (5 times) and stir the reaction solution overnight at 100°C. Partition the reaction solution between EtOAc and brine (1+1) and extract the separated aqueous layer 3 times with EtOAc. Wash combined organic layer with brine and dry with Na$_2$SO$_4$. Remove solvent under reduced pressure and purify the crude product by preparative radial chromatography (silica gel 60PF, CyH/EtOAc 3+1) to obtain (2'-Amino-biphenyl-3-yl)-acetic acid methyl ester (71) as an orange oil (304mg, 81%). ^{1}H NMR (400MHz, CDCl$_3$): 3.66 (s, 2 H); 3.69 (s, 3 H); 3.62-3.86 (br.s, 2 H); 6.75 (d, 1 H, J = 8.1Hz); 6.80 (t, 1 H, J = 7.3Hz); 7.11 (d, 1 H, J = 7.3Hz); 7.15 (d, 1 H, J = 8.1Hz); 7.22-7.26 (br.m, 1 H); 7.32-7.42 (m, 3 H).

Step 2: (The following reaction is done in an anhydrous N_2 atmosphere.) Suspend EDC·HCl (61mg, 0.32mmol) and Et$_3$N (44μL, 0.32mmol) in anhydrous DCM (1.0mL) and stir the resulting solution for 5min at rt. Add 3-(3,4,5-Trimethoxy-phenyl)-propionic acid

- 51 -

(55mg, 0.23mmol) and DMAP (2mg, 0.02mmol) and stir the resulting solution for 15min. Add (2'-Amino-biphenyl-3-yl)-acetic acid methyl ester (71) (50mg, 0.21mmol) and stir the reaction solution overnight at rt. Quench reaction solution with water, separate layers and extract aqu. layer with DCM (3 times). Wash combined organic layer with brine and dry

5   with Na$_2$SO$_4$. Purify the crude product by preparative radial chromatography (silica gel, EtOAc/CyH 1+1) to obtain {2'-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-biphenyl-3-yl}-acetic acid methyl ester (72) (46mg, 48%) as a yellow oil. ^{1}H NMR (400MHz, CDCl$_3$): 2.50 (t, 2 H, J = 7.6Hz); 2.90 (t, 2 H, J = 7.7Hz); 3.64 (s, 2 H); 3.65 (s, 3 H); 3.77 (s, 6 H); 3.78 (s, 3 H); 6.38 (s, 2 H); 7.09-7.18 (m, 3 H); 7.19-7.28 (m, 3 H); 7.34 (d, 1 H, J =

10   8.1Hz); 7.38 (d, 1 H, J = 7.8Hz); 8.31 (br.d, 1 H, J = 7.8Hz).

Step 3: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve {2'-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-biphenyl-3-yl}-acetic acid methyl ester (72) (46mg, 0.10mmol) in anhydrous DCM (1.0mL), cool the solution to −78°C and add dropwise BBr$_3$ (85μL, 0.90mmol). Stir the reaction mixture for 30min at −78°C and after

15   slowly warming up for additional 2h at rt. Add dropwise ice water, separate layers and extract aqu. layer with DCM (3 times). Wash combined organic layer with brine and dry with Na$_2$SO$_4$.. Purify the crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain {2'-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-biphenyl-3-yl}-acetic acid methyl ester (73) (2mg, 5%). ^{1}H NMR (400MHz, CD$_3$CN): 2.43 (t, 2 H, J =

20   7.6Hz); 2.69 (t, 2 H, J = 7.6Hz); 3.66 (s, 3 H); 3.70 (s, 2 H); 6.25 (s, 2 H); 7.18-7.34 (m, 5 H); 7.35-7.44 (m, 2 H); 7.65 (br.s, 1 H); 7.89 (br.d, 1 H, J = 8.3Hz).

EXAMPLE 9

25   **4-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-cyclohexanecarboxylic acid**

(76)

SCHEME 16
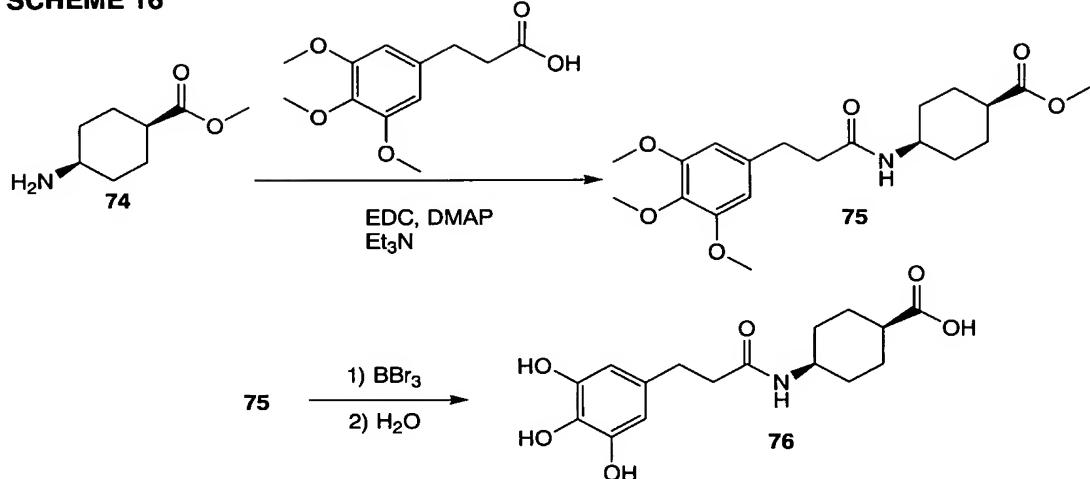
Step 1: (The following reaction is done in an anhydrous N_2 atmosphere.) Suspend EDC·HCl (175mg, 0.91mmol) and Et_3N (127μL, 0.91mmol) in anhydrous DCM (8.0mL) and stir the resulting solution for 5min at rt. Add 3-(3,4,5-Trimethoxy-phenyl)-propionic acid (219mg, 0.91mmol) and DMAP (22mg, 0.18mmol) and stir the resulting solution for 10min. Add cis-4-Amino-cyclohexanecarboxylic acid methyl ester (74) (136mg, 0.87mmol) and stir the reaction solution 2d at rt. Remove solvent and purify the crude product by flash chromatography (silica gel, EtOAc/CyH 3+1, later EtOAc) to obtain cis-{ 4-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-cyclohexanecarboxylic acid methyl ester (75) (254mg, 76%) as a colorless viscous oil. ^{1}H NMR (400MHz, CDCl$_3$): 1.40-1.51 (m, 2 H); 1.59-1.70 (m, 4 H); 1.70-1.82 (m, 2 H); 2.40-2.48 (m, 3 H); 2.88 (t, 2 H, J = 7.6Hz); 3.65 (s, 3 H); 3.79 (s, 3 H); 3.82 (s, 6 H); 3.86-3.95 (m, 1 H); 5.33 (br.d, 1 H, J = 7.3Hz); 6.40 (s, 2 H).

Step 2: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve cis-{ 4-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-cyclohexanecarboxylic acid methyl ester (75) (82mg, 0.21mmol) in anhydrous DCM (2.0mL), cool the solution to −78°C and add dropwise BBr$_3$ (205μL, 2.17mmol). Stir the reaction mixture for 20min at −78°C and after slowly warming up for additional 2h at rt. Add dropwise water, followed by DCM and MeOH and remove solvent. Purify the crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain cis-4-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-cyclohexanecarboxylic acid (76) (7mg, 10%) as a colorless sticky solid.

^{1}H NMR (400MHz, CD$_3$OD): 1.47-1.60 (m, 2 H); 1.62-1.73 (m, 4 H); 1.91-2.02 (m, 2 H);

2.42 (t, 2 H, J = 7.6Hz); 2.47-2.54 (m, 1 H); 2.71 (t, 2 H, J = 7.3Hz); 3.75-3.84 (m, 1 H);

6.23 (s, 2 H).

EXAMPLE 10

4-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-benzoic acid (79)

SCHEME 17
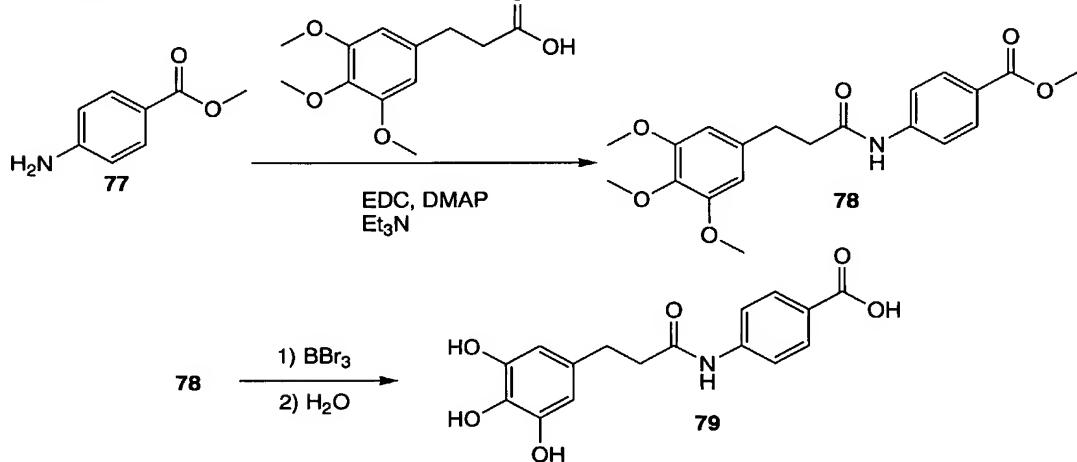
Step 1: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Suspend
EDC·HCl (80mg, 0.41mmol) and Et$_3$N (58μL, 0.41mmol) in anhydrous DCM (2.0mL) and
stir the resulting solution for 5min at rt. Add 3-(3,4,5-Trimethoxy-phenyl)-propionic acid
(70mg, 0.29mmol) and DMAP (5mg, 0.04mmol) and stir the resulting solution for 10min.
Add 4-Amino-benzoic acid methyl ester (77) (42mg, 0.27mmol) and stir the reaction
solution 2d at rt. Quench reaction solution with water, separate layers and extract aqu.
layer with DCM (3 times). Wash combined organic layer with brine, dry with Na$_2$SO$_4$ and
filtrate it through a short pad of silica gel using EtOAc to obtain 4-[3-(3,4,5-Trimethoxy-
phenyl)-propionylamino]-benzoic acid methyl ester (78) (91mg, 88%) as a white solid. No
further purification. ^{1}H NMR (400MHz, CDCl$_3$): 2.60 (t, 2 H, J = 7.6Hz); 2.91 (t, 2 H, J =

- 54 -

7.6Hz); 3.70 (s, 6 H); 3.76 (s, 3 H); 3.83 (s, 3 H); 6.35 (s, 2 H); 7.55 (d, 2 H, J = 8.3Hz); 7.91 (d, 2 H, J = 8.6Hz); 8.09 (s, 1 H).

       Step 2: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve 4-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-benzoic acid methyl ester (78) (45mg,

5   0.12mmol) in anhydrous DCM (1.2mL), cool the solution to −78°C and add dropwise BBr₃ (90μL, 0.96mmol). Stir the reaction mixture for 30min at −78°C and after slowly warming up for additional 3h at rt. Add dropwise ice-water/THF (1+1) followed by MeOH and remove solvent. Purify the crude product by preparative RP HPLC (gradient, water/CH₃CN 95:5 to 5:95) to obtain 4-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-

10 benzoic acid (79) (17mg, 44%) as a white solid. ¹H NMR (400MHz, CD₃OD): 2.65 (t, 2 H, J = 7.5Hz); 2.83 (t, 2 H, J = 7.5Hz); 6.29 (s, 2 H); 7.68 (d, 2 H, J = 8.3Hz); 7.99 (d, 2 H, J = 8.6Hz).

<div align="center">

EXAMPLE 11

15

(5-{2-[(3',4',5'-Trihydroxy-biphenyl-2-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic acid (87)

</div>

SCHEME 18
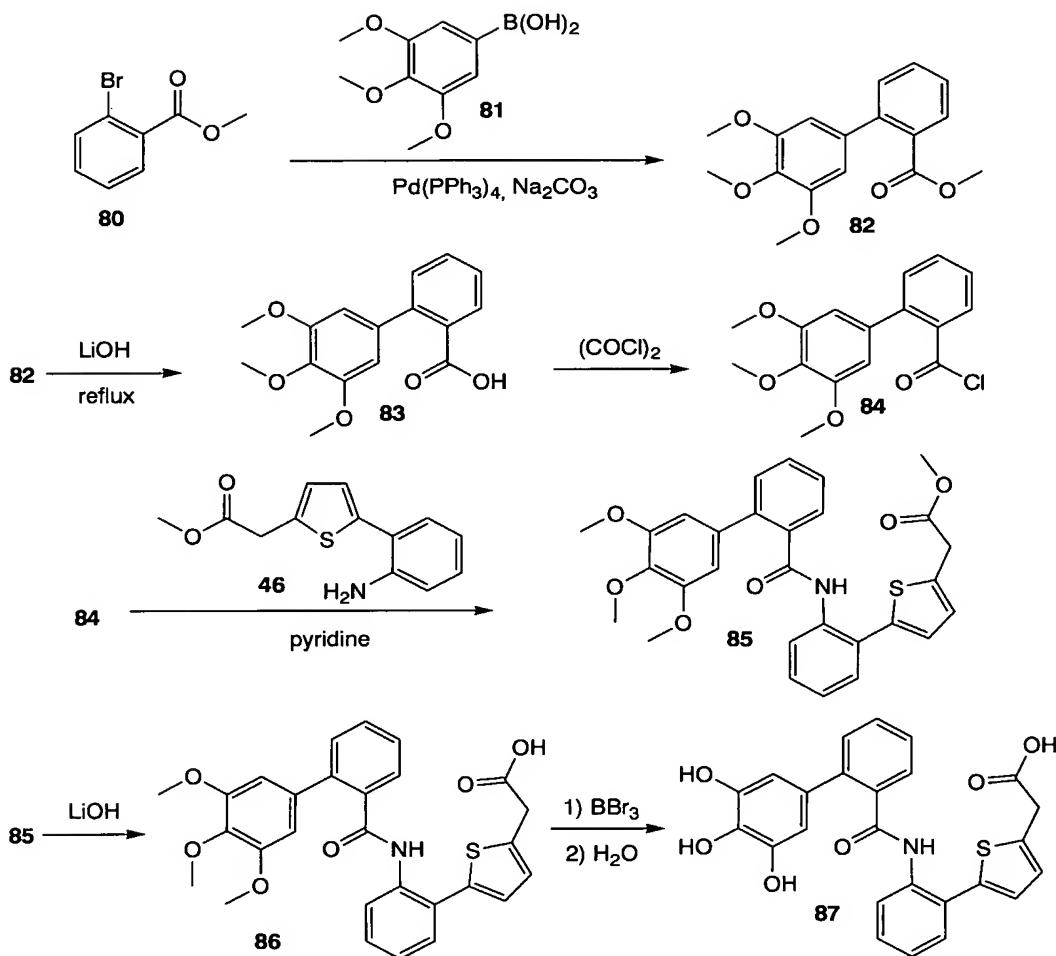
Step 1: (The following reaction is done in an N_2 atmosphere.) To a solution of Methyl-2-bromobenzoate (80) (922mg, 4.29mmol) in toluene (11mL) is added Pd(PPh$_3$)$_4$ (297mg, 0.26mmol) and Na$_2$CO$_3$·10H$_2$O (3.43g, 12.00mmol) in water (3.8mL). Degas the resulting mixture is carefully (5 times alternating vacuum and flushing with N_2). Add a solution of 3,4,5-Trimethoxyphenylboronic acid (81) (1.00g, 4.72mmol) in toluene (10mL) by syringe, degas the resulting mixture again carefully and stir the resulting mixture overnight at 100°C. Partition the mixture between brine/EtOAc (1+1), separate layers, extract the aqu. layer with EtOAc (3x), wash the combined organic layer with brine and dry with Na$_2$SO$_4$. Purify the crude product by flash chromatography (silica gel, EtOAc/CyH 1+7, later 1+5) to obtain 3',4',5'-Trimethoxy-biphenyl-2-carboxylic acid methyl ester (82) as a yellow solid (1.30g, 99%). ^{1}H NMR (400MHz, CDCl$_3$): 3.65 (s,

3 H); 3.84 (s, 6 H); 3.87 (s, 3 H); 6.52 (s, 2 H); 7.35 – 7.42 (m, 2 H); 7.50 (t, 1 H,
J = 8.0Hz); 7.73 (d, 1 H, J = 8.0Hz).

Step 2: Dissolve 3',4',5'-Trimethoxy-biphenyl-2-carboxylic acid methyl ester (82)
(626mg, 2.08mmol) in MeOH (14mL) at rt and add 1M aqu LiOH (4.2mL, 4.20mmol). Stir
reaction mixture for 8h under reflux. Remove solvent and partition the residue between 1M
aqu. HCl and EtOAc, separate layers, extract the aqu. layer with EtOAc (3x), wash the
combined organic layer with brine and dry with Na_2SO_4. Remove solvent and recrystallize
residue from EtOAc/CyH 1+2 to obtain 3',4',5'-Trimethoxy-biphenyl-2-carboxylic acid
(83) as a white solid (423mg, 79%). ^{1}H NMR (400MHz, CD_3OD: 3.84 (s, 3 H); 3.89 (s,
6 H); 6.68 (s, 2 H); 7.42 – 7.49 (m, 2 H); 7.57 (t, 1 H, J = 7.5Hz); 7.76 (d, 1 H, J = 8.0Hz).

Step 3: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve
3',4',5'-Trimethoxy-biphenyl-2-carboxylic acid (83) (54mg, 0.18mmol) in anhydrous DCM
(1.3mL) and add anhydrous DMF (1 drop, cat. amount). Then add slowly oxalyl chloride
(21μL, 0.24mmol) by keeping temperature at ca. 20°C with a water bath and stir the turbid
mixture for additional 2h at rt. Remove solvent and dry in vacuum to obtain crude 3',4',5'-
Trimethoxy-biphenyl-2-carbonyl chloride (84) as a yellow solid. No further purification.

Step 4: Add a solution of 3',4',5'-Trimethoxy-biphenyl-2-carbonyl chloride (84)
(0.18mmol) in DCM (1.0mL) to an ice cooled solution of [5-(2-Amino-phenyl)-thiophen-
2-yl]-acetic acid methyl ester (46) (46mg, 0.18mmol) in anhydrous DCM (2.0mL) and
anhydrous pyridine (0.5mL). Stir the reaction mixture for 1h at 0°C and additional 20h at
rt. Pour the reaction mixture into ice cooled 1M aqu. HCl, extract with EtOAc (2x) and
DCM (2x), wash the combined organic layer with brine and dry with Na_2SO_4. Purify the
crude product by preparative radial chromatography (silica gel, EtOAc/CyH 1+2) to obtain
(5-{2-[(3',4',5'-Trimethoxy-biphenyl-2-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic
acid methyl ester (85) as a light brown solid (58mg, 59%). ^{1}H NMR (400MHz, $CDCl_3$):
3.70 (s, 3 H); 3.76 (s, 6 H); 3.78 (s, 2 H); 3.80 (s, 3 H); 6.29 (d, 1 H, J = 3.4Hz); 6.60 (s,
2 H); 6.75 (d, 1 H, J = 3.4Hz); 7.07 (t, 1 H, J = 7.6Hz); 7,23 (d, 1 H, J = 7.6Hz); 7.31 (t,
1 H, J = 8.0Hz); 7.37 –7.43 (m, 2 H); 7.48 (t, 1 H, J = 7.6Hz); 7.52 (s, 1 H); 7.69 (d, 1 H,
J = 8.0Hz); 8.45 (d, 1 H, J = 8.0Hz).

Step 5: Dissolve (5-{2-[(3',4',5'-Trimethoxy-biphenyl-2-carbonyl)-amino]-
phenyl}-thiophen-2-yl)-acetic acid methyl ester (85) (56mg, 0.11mmol) in MeCN (3.8mL)

at rt and add 1M aqu LiOH (760μL, 0.76mmol). Stir reaction mixture 18h at rt. Quench reaction mixture (cooling bath) with 2M aqu. HCl. Extract the mixture with EtOAc (3x), wash the combined organic layer with brine and dry with Na_2SO_4 to obtain (5-{2-[(3',4',5'-Trimethoxy-biphenyl-2-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic acid (86) (55mg,

5   99%) as a brown solid. ^{1}H NMR (400MHz, CDCl$_3$): 3.76 (s, 6 H), 3.80 (s, 3 H); 3.83 (s, 2 H); 6.32 (d, 1 H, J = 3.5Hz); 6.60 (s, 2 H); 6.78 (d, 1 H, J = 3.5Hz); 7.07 (t, 1 H, J = 7.6Hz); 7.23 (d, 1 H, J = 7,6Hz); 7.32 (t, 1 H, J = 7.6Hz); 7.36 – 7.54 (m, 3 H); 7.69 (d, 1 H, J = 8.0Hz); 8.43 (d, 1 H, J = 8.0Hz).

Step 6: (The following reaction is done in an anhydrous N_2 atmosphere.) Dissolve

10   (5-{2-[(3',4',5'-Trimethoxy-biphenyl-2-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic acid (86) (55mg, 0.11mmol) in anhydrous DCM (3.2mL) at -78°C, add dropwise a 1M solution of BBr$_3$ in DCM (730μL, 0.73mmol) and stir for additional 30min at –78°C. After slowly warming up stir the reaction solution for additional 4h at rt. Cool reaction mixture to 0°C, add dropwise water. Extract the mixture with EtOAc (3x), wash combined organic

15   layer with brine and dry it with Na_2SO_4. Purify the crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain (5-{2-[(3',4',5'-Trihydroxy-biphenyl-2-carbonyl)-amino]-phenyl}-thiophen-2-yl)-acetic acid (87) (10mg, 18%) as a yellow solid. ^{1}H NMR (400MHz, CD$_3$OD): 3.88 (s, 2 H); 6.50 (s, 2 H); 6.66 (d, 1 H, J = 3.5Hz); 6.93 (d, 1 H, J = 3.5Hz); 7.23 (t; 1 H, J = 7.3Hz); 7.35 (t, 1 H, J = 7.6 Hz); 7.38 –7.46 (m, 3 H);

20   7.50 (t, 1 H, J = 7.3Hz); 7.62 (d, 1 H, J = 8.0Hz); 7.84 (d, 1 H, J = 8.0Hz).

EXAMPLE 12

3-{3-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-phenylamino}-benzoic

25   **acid (92)**

SCHEME 19
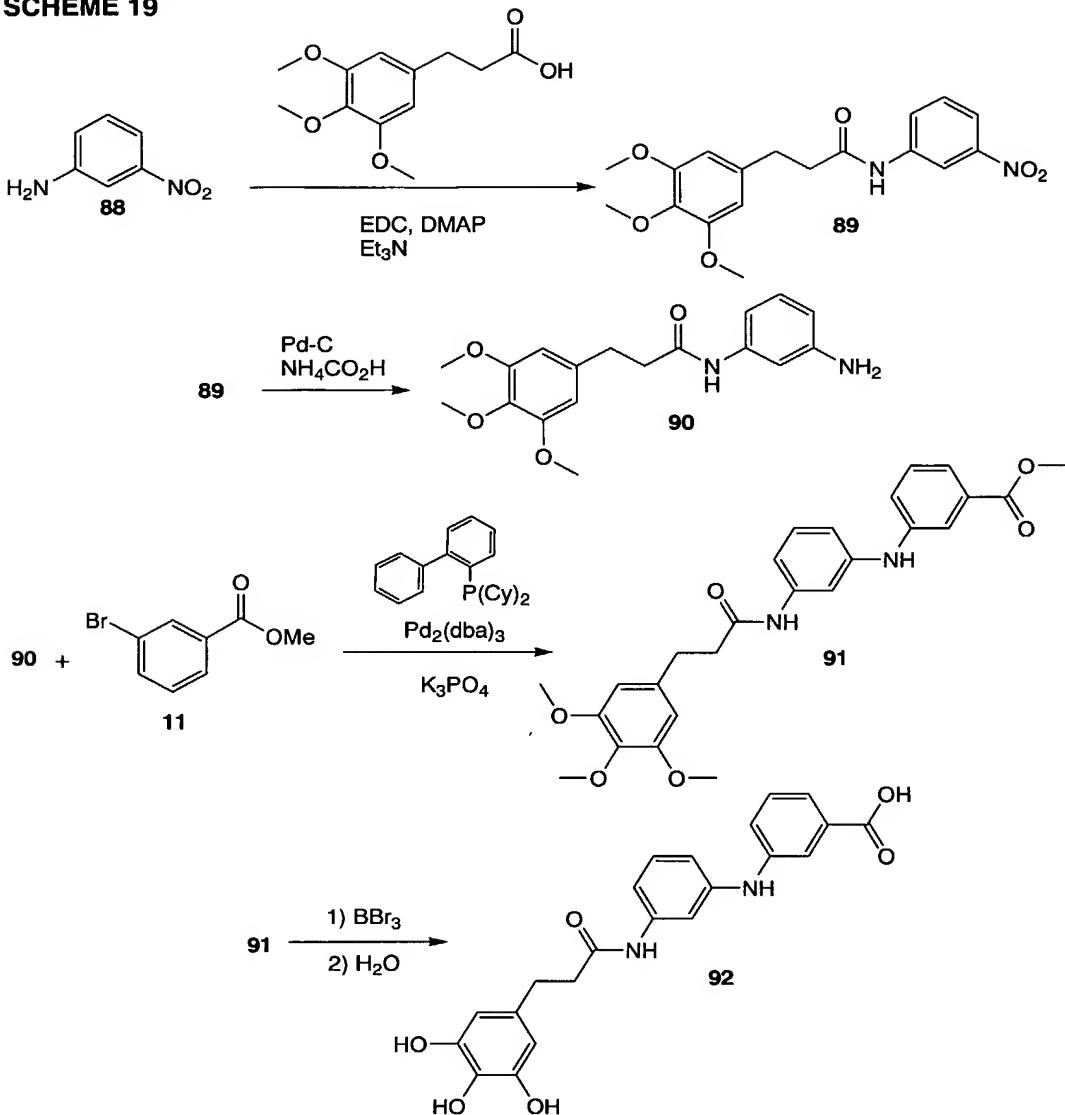
Step 1: (The following reaction is done in an anhydrous N_2 atmosphere.) Suspend EDC·HCl (402mg, 2.10mmol) and Et$_3$N (293μL, 2.10mmol) in anhydrous DCM (17mL) and stir the resulting solution for 5min at rt. Add 3-(3,4,5-Trimethoxy-phenyl)-propionic acid (480mg, 2.00mmol) and DMAP (24mg, 0.20mmol) and stir the resulting solution for 5min. 3-Nitro-phenylamine (88) (414mg, 3.00mmol) and stir the reaction solution 24h at rt. Quench reaction solution with sat. aqu. NH$_4$Cl and water, separate layers and extract aqu. layer with EtOAc (3 times). Wash combined organic layer with brine and dry with Na$_2$SO$_4$. Purify the crude product by preparative radial chromatography (silica gel, EtOAc/CyH 1+1) to obtain N-(3-Nitro-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propionamide

(89) (508mg, 70%) as a yellow solid. ^{1}H NMR (400MHz, CDCl$_3$): 2.65 (t, 2 H, J = 7.5Hz); 2.98 (t, 2 H, J = 7.5Hz); 3.79 (s, 6 H); 3.81 (s, 3 H); 6.42 (s, 2 H); 7.41 (s, 1 H); 7.45 (t, 1 H, J = 8.3Hz); 7.84 (d, 1 H, J = 8.3Hz); 7.92 (d, 1 H, J = 8.3 Hz); 8.31 (s, 1 H).

Step 2: (The following reaction is done in an N$_2$ atmosphere.) Dissolve N-(3-Nitro-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propionamide (89) (100mg, 0.28mmol) in MeOH (4.5mL) and add Pd on carbon (10% (w/w) Pd content, 29.5mg, 0.028mmol) followed by NH$_4$CO$_2$H (175mg, 2.77mmol) at rt. Degas the reaction mixture carefully (flush with N$_2$) and stir it for 75min at rt. Filtrate reaction mixture through a short pad of celite and remove solvent. Treat residue with EtOAc, filtrate again through a short pad of celite and remove solvent to obtain N-(3-Amino-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propionamide (90) (91 mg, 99%) as a white solid. No further purification. ^{1}H NMR (400MHz, CD$_3$OD): 2.65 (t, 2 H, J = 7.5Hz); 2.98 (t, 2 H, J = 7.5Hz); 3.75 (s, 3 H); 3.82 (s, 6 H); 6.50 (dd, 1 H, J_1 = 8.0Hz, J_2 = 2.0Hz); 6.58 (s, 2 H); 6.80 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 2.0Hz); 7.02 – 7.07 (m, 1 H); 7.04 (t, 1 H, J = 8.0 Hz).

Step 3: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Charge a 2-necked round buttom flask with Pd$_2$(dba)$_3$ (5.5mg, 0.006mmol), 2-(Dicyclohexylphosphino)biphenyl (2mg, 0.005mmol), Methyl-3-bromobenzoate (11) (51mg, 0.24mmol) and potassium phosphate (71mg, 0.33mmol) and degas it carefully (flush with N$_2$). Add a solution of N-(3-Amino-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propionamide (90) (91mg, 0.27mmol) in dry degassed DME (1.0mL) and and stir the resulting mixture for 15h at 85°C. Cool the reaction suspension to rt, dilute it with EtOAc, filtrate through a short pad of celite and remove solvent. Purify the crude product preparative radial chromatography (silica gel, EtOAc/CyH 1+1) to obtain 3-{3-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-phenylamino-benzoic acid methyl ester (91) (97mg, 87%) as a yellow solid. ^{1}H NMR (400MHz, (CD$_3$)$_2$SO): 2.59 (t, 2 H, J = 7.8Hz); 2.83 (t, 2 H, J = 7.8Hz); 3.60 (s, 3 H), 3.72 (s, 6 H); 3.82 (s, 3 H); 6.54 (s, 2 H); 6.75 (d, 1 H, J = 7.8 Hz); 7.07 (d, 1 H, J = 8.0Hz); 7.16 (t, 1 H, J = 8.0 Hz); 7.29 – 7.40 (m, 3 H); 7.48 (s, 1 H), 7.63 (s, 1 H); 8.40 (s, 1 H); 9,83 (s, 1 H).

Step 4: (The following reaction is done in an anhydrous N$_2$ atmosphere.) Dissolve 3-{3-[3-(3,4,5-Trimethoxy-phenyl)-propionylamino]-phenylamino-benzoic acid methyl ester (91) (36mg, 0.08mmol) in anhydrous DCM (2.3mL) at -78°C, add dropwise a 1M

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solution of BBr$_3$ in DCM (930μL, 0.93mmol) and stir for additional 30min at –78°C. After slowly warming up stir the reaction solution for additional 4h at rt. Cool reaction mixture to 0°C, add dropwise water/THF (1+1) and remove solvent. Purify the crude product by preparative RP HPLC (gradient, water/CH$_3$CN 95:5 to 5:95) to obtain 3-{3-[3-(3,4,5-Trihydroxy-phenyl)-propionylamino]-phenylamino}-benzoic acid (92) (10mg, 33%) as a white solid. ^{1}H NMR (400MHz, CD$_3$OD): 2.60 (t, 2 H, J = 7.7Hz); 2.85 (t, 2 H, J = 7.7Hz); 6.29 (s, 2 H); 6.70 (dd, 1 H, J_1 = 8.0Hz, J_2 = 2.0Hz); 7.06 (d, 1 H, J = 8.0Hz), 7.21 (t, 1 H, J = 8.0Hz), 7.33 – 7.37 (m, 2 H), 7.45 (m$_c$, 1 H); 7.50 – 7.54 (m, 1 H); 7.77 (s, 1 H).

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The compounds referred to in the following SCHEME20 are those compounds referred to as the particularly preferred compounds herein.

SCHEME 20
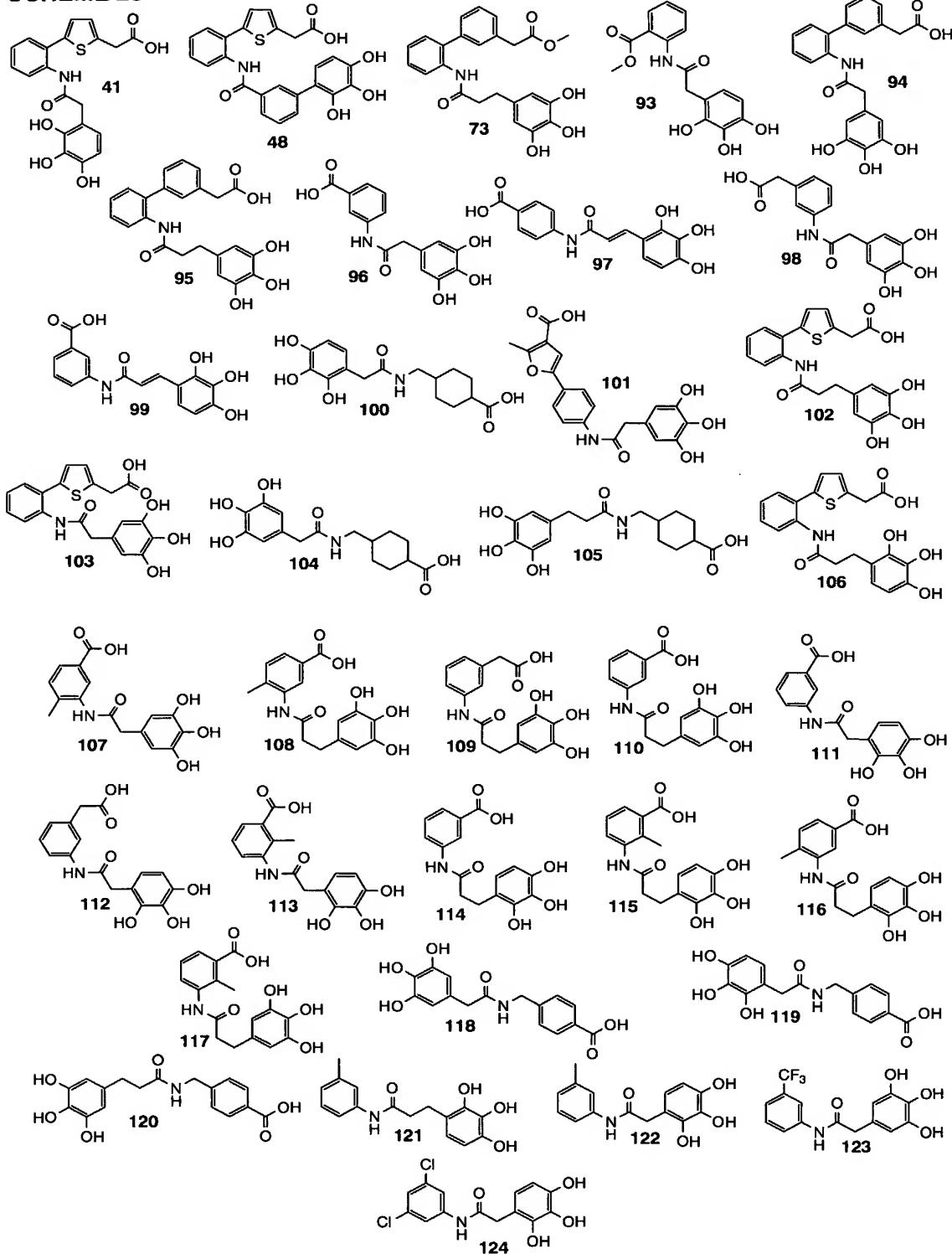
Sialyl Lewis^x Tyrosine Sulfate Assay (sLe^x TSA):

Compounds of the present invention are assayed on a molecular level for their ability to inhibit the binding of P-, L-, or E-selectin chimeric molecules to sLe^x and tyrosinesulfate residues linked to a polymeric matrix as a PSGL-1 substitute. Selected 50% inhibitory

5   concentrations (IC$_{50}$-values) are determined.

Microtiter plates are coated overnight in carbonate buffer pH9,6 with goat anti human Fc
mAB (10 μg/ml). After washing in assay buffer (25mM 4-(2-hydroxyethyl)-1-
piperazineethanesulfonic acid (HEPES), 150mM NaCl, 1mM CaCl$_2$ pH7,4) and blocking
(3% bovine serum albumin (BSA) in assay buffer) plates are incubated for 2h at 37°C with

10   human P-Selectin-IgG-chimera (0,61nM respectively 150ng/mL) or human L-Selectin-
IgG-chimera (0,61nM respectively 89ng/mL) or human E-Selectin-IgG-chimera (0,61nM
respectively 131ng/mL). 5μl of sLe^x -tyrosine sulfate polyacrylamide (1mg/ml) carrying
15% sLe^x, 10% Tyrosine-sulfate and 5% biotin is complexed with 20μl Streptavidin-
Peroxidase solution (1mg/ml) and 25μl assay buffer without CaCl$_2$. For use in the assay,

15   the ligand complex is diluted 1:10000 in assay buffer and further diluted 1:1 with varying
amounts of compounds in assay buffer incl. 2%DMSO. This mixture is added to the wells
precoated with E- or P-selectin. After incubation for 2h at 37°C, wells are washed for six
times with in assay buffer incl. 0,005% Polyoxyethylenesorbitan monolaurate (TWEEN
20), developed for 10-15min with 20μl 3,3',5,5'-tetramethylbenzidine (TMB)/H$_2$O$_2$

20   substrate solution and stopped with 20μl 1M H$_2$SO$_4$. Bound sLe^x -Tyrosine sulfate ligand
complex is determined by measuring optical density at 450nm vs. 620nm in a Fusion
alpha-FP reader (sold from Packard Bioscience, Dreieich, Germany).

Table of sLe TSA Data; _in vitro_-Inhibition of E-/P-/L-Selectin at 100 μM			
Compound	E-Selectin [% Inhib.]	P-Selectin [% Inhib.]	L-Selectin [% Inhib.]
41	46	92	81
48	31	97	95
73	54	84	88
93	20	68	63
94	79	78	76
95	89	90	81
96	63	86	73
97	51	97	98
98	58	57	52
99	71	99	99
100	21	40	27
101	50	93	95
102	99	97	96
103	68	87	81
104	67	67	62
105	90	86	84
106	52	94	85
107	53	87	75
108	85	86	84
109	82	73	72
110	96	96	92
111	46	99	97
112	38	97	83
113	42	73	48
114	38	99	95
115	n.a.	89	88
116	92	88	87
117	94	86	89
118	53	79	66
119	14	82	55
120	92	88	87
121	29	73	77
122	70	81	87

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Results from sLe^xTSA: IC$_{50}$ Data for E-/ P-/ L-Selectin

Compound	IC$_{50}$ E-Selectin [μM]	IC$_{50}$ P-Selectin [μM]	IC$_{50}$ L-Selectin [μM]
41	-	7.6	14.6
48	132	5.8	9.8
94	4.9	4.2	8.7
96	0.8	1.1	1.4
97	285	3.5	6.2
98	1.0	2.1	-
99	-	14.4	24.9
102	3.3	2.4	3.1
104	3.0	2.8	3.3
105	3.1	3.4	5.7
108	1.3	1.7	1.8
109	2.3	2.3	2.3
111	0.6	2.1	7.0
112	-	3.7	9.9
115	-	7.4	16.0
116	7.3	13.0	15.0
117	8.4	21.7	109
118	8.7	14.8	26.2
120	8.4	34.9	30.8

Flow Chamber Assay / Cell Adhesion and Rolling under Flow Conditions

To assess the capability of compounds to inhibit cell binding under dynamic conditions resembling the flow in a blood vessel, flow chamber assays addressing/ testing binding of HL-60 cells / various cell lines to P-selectin, L-selectin and E-selectin chimeric molecules are performed.

Cell attachment under flow conditions are determined using a parallel flow chamber system. A 35mm polystyrene culture dish is coated for 1 hour at room temperature with coating buffer (50mM tris-(hydroxymethyl) aminomethane buffer (Tris), 150 mM NaCl, 2 mM $CaCl_2$; pH 7,4) containing human E- or P-selectin-IgG chimera at concentrations of 2,5µg/ml or 10µg/ml, respectively. After removal of the coating solution non specific binding sites are blocked for an additional hour with 1% BSA in coating buffer at room temperature. After washing with assay buffer ("Roswell Park Memorial Institute 1640" (RPMI 1640) + 10mM HEPES) the dish is fitted into a parallel plate laminar flow chamber (sold from Glycotech, Rockville, MD) and mounted on an inverted phase-contrast microscope (sold from Olympus, Hamburg, Germany) equipped with a CCD camera (JVC) that is connected to a PC. Employing a peristaltic pump (sold from Ismatec, Wertheim-Mondfeld, Germany) the re-circulating system is equilibrated with assay buffer containing 125µM compound or vehicle control (DMSO). Cells (1 million / ml) are added to the chamber and allowed to distribute for 2 minutes at a high flow rate. The flow rate is then decreased resulting in a calculated flow shear of 1 dyne/cm^2. Video sequences of 10 low power fields are digitally recorded after 5 minutes continuous flow. The percentage of inhibition is calculated from the mean number of cells per field that attached to the coated dish surface in the presence versus absence of compound of at independent experiments.

Data from Flow Chamber Assay for E- and P-Selectin

Compound	E-Selectin [% Inhib.]	P-Selectin [% Inhib.]
41	26	-
48	61	55
97	-	47
99	28	96
101	-	99
102	35	11
108	n.a.	17
118	16	20
120	21	21
121	18	44
122	27	22
123	51	-
124	28	23

Parallel Artificial Membrane Permeation Assay (PAMPA)

5 The test compounds are dissolved at 10mM in DMSO and diluted to 500μM with PBS pH 7.4 or pH 4.0, respectively resulting in `donor solutions´. For use as an artificial membrane, a 1% solution of lecithin (w/v) in dodecane is prepared and sonicated. Then, 5 μl of the lecithin/dodecane mixture are carefully pipetted into each donor plate well. Immediately after the application of the artificial membrane, 150 μl of drug containing donor solutions are added to each well of the donor plate. Each well of the acceptor plate is

10 filled with 300 μl buffer (PBS with 5% DMSO at pH 7.4 or pH 4.0, respectively) and the drug-filled donor plate is placed onto the acceptor plate, making sure the membrane is in contact with the buffer. After replacement of the lid, the assembled plates are transferred into a sealed box equipped with a moistured towel and incubated at room temperature for 16 hours. Then, the wells of the acceptor plate are analyzed with LC/MS.

15

Data from PAMPA

Compound	[% flux] at pH 4.0	[% flux] at pH 7.4
93	0	17
97	0	16
118	0	1
121	12	12
122	6	0
123	27	0
124	100	0